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THE COLLOIDAL GOLD REACTION IN THE CEREBROSPINAL FLUID.*

By Sydney R. Miller, M. D., and Robert L. Levy, M. D.

(From the Laboratory of Internal Medicine, The Henry Phipps Psychiatric Clinic, and the Medical Clinic of The Johns Hopkins Hospital.)

1. Introduction.

The examination of the cerebro-spinal fluid is essential in the study of many neurological and psychiatrical conditions. From it much information of diagnostic and prognostic importance is obtained, while recent studies, notably by Swift and Ellis,[1] indicate that it is a valuable index of the efficacy of treatment, particularly the specific therapy of syphilitic diseases of the central nervous system. Much doubt still exists as to the exact nature, origin and composition of spinal fluid, though the investigations of Dandy and Blackfan,[2] Dixon and Halliburton[3] and others promise much for the final answer to these problems. Particularly is opinion divided over the form and combinations of proteins which occur in normal and abnormal fluids. Physical-chemical methods thus far have failed to yield results of more than theoretical value and the same may be said of pure chemistry. The occurrence of ferments, investigated by Kafka[4] and Szabó,[5] while of interest, is yet of doubtful clinical value, and Abderhalden's[6] serodiagnostic method is still in a somewhat experimental and empirical state, quite apart from the fact that its performance is attended with many difficulties and numerous possible sources of error. There are many obstacles in the way of spinal fluid analysis, notably the fact that its withdrawal, even in small amounts, from normal individuals is not infrequently followed by unpleasant symptoms. The introduction therefore of a method of study which requires minimal amounts of fluid is greatly to be desired, since only by an exact acquaintance with the normal can we hope to appreciate deviations from it.

There are three findings in the spinal fluid of recognized diagnostic value; first, a positive Wassermann reaction; second, an increased cell count, and third, an increased protein content, commonly referred to in the literature as the Phase 1 of Nonne. The Wassermann reaction, negative in nearly all fluids examined during the first three stages of syphilis, becomes increasingly positive when applied to cases of cerebro-spinal lues, tabes and paresis, averaging between 90% and 100% positive in the last condition. Opinion is still somewhat divided as to the best method of investigation of the cellular elements, most workers being content with a simple quantitative estimation of their increase, while others, as Alzheimer[7] and Szécsi,[8] rely more upon qualitative changes as revealed by histological and staining methods. Nonne's[9] Phase I, modified by numerous workers, notably Ross and Jones[10] and Noguchi,[11] represents nothing more than a pro-

*Read before the Johns Hopkins Hospital Medical Society, March 2, 1914.

tein-complex group reaction, though it is commonly accepted, when positive, as indicating an increase in the globulin content of the fluid. That globulins in abnormal fluids constitute only a part of the precipitate caused by one-half saturation with ammonium sulphate can readily be demonstrated. Although positive in from 95% to 100% of luetic infections of the central nervous system, Phase I alone does not enable one to differentiate between luetic and non-luetic conditions. It is incorrectly stated that the intensity of the reaction is always greater in the specific infections. While these three tests meet most of the requirements of clinical diagnosis, they tell us nothing concerning the factors responsible for their causation.

The present report deals with one of the recent tests applied to the spinal fluid, in which colloidal chemistry plays the leading rôle. In view of the wide range to which the relatively new subject of colloidal chemistry is applied, and the exactness of the laws which control and determine colloidal reactions, and their extreme delicacy, it is not surprising that this science should have found a place in clinical laboratory methods. If the predictions of such investigators as Ostwald are to be relied upon, we may ultimately expect to learn most concerning the aggregation of living protoplasm, the laws which govern immunity, the basis for the Wassermann reaction, etc., by the use of colloidal chemistry and allied sciences.

The foundation for the present test was laid by Zsigmondy [12] in 1901. Having worked exhaustively with solutions of colloidal gold, he attempted with success to use it as a means for the quantitative estimation of protein substances. It was well known that colloidal solutions of gold or other metals are precipitated or "coagulated out" by electrolytes, this coagulation depending upon the degree of concentration as well as the valency of the electrolytes employed. It was also recognized that colloids are electrically charged and that two oppositely charged colloids mutually precipitate one another, though only in definite quantitative amounts. If these amounts are exceeded in one way or the other, no precipitation occurs. Zsigmondy discovered that solutions of proteins give protection to colloidal solutions of gold up to a certain point, and he determined the so-called *Goldzahl* for various protein substances, by which is meant the number of milligrams of the protein employed, just sufficient to prevent the precipitation of 10 cc. of colloidal gold of a percentage of .0053 in the presence of 1 cc. of 10% NaCl solution. By this method it can be determined whether a given protein is absolutely pure, or granted this is the case, how much is present in a given solution. In attempting to apply this gold protection method to the study of the proteins of the spinal fluid, Lange,[13] in 1912, discovered that instead of securing protection, quite the reverse occurred, particularly in conditions in which the spinal fluid contained an abnormal amount of protein substance, notably in the syphilitic diseases of the central nervous system. Moreover, he observed that the reaction which occurred took place within certain dilution limits which seemed to be more or less specific, thus making possible, by means of colloidal solutions of gold, the differentiation between syphilitic and non-syphilitic conditions. Since that time, the test as used by various observers has yielded fairly consistent results, which will be discussed in more detail in another portion of the present report.

2. Apparatus and Solutions Required.

A. Glassware.

For the preparation of all reagents required, the following Jena glassware is necessary:

1. Flasks: 1000 cc., plain and distilling, the latter provided with side glass outlet tube.
2. Certified graduates: 25 and 1000 cc.
3. Beakers: 1 and 2 litre sizes.
4. Liebig condensers: all glass.
5. Glass stoppered stock solution bottles, 2 litres. With the exception of the condensers, all glassware is rinsed with strong HCl, followed by distilled water and hot air sterilization for 20 minutes. Condensers are cleaned with steam and rinsed by the first 200 cc. of the distillate, which is subsequently thrown away.

In the actual performance of the test there are needed:

1. Test tubes: 120x12 mm., thick walled.
2. Certified pipettes: 1, 10, 25 cc.

The tubes are cleaned each time by boiling in 10% potassium bichromate solution, and then in distilled water, using a brush when necessary, to remove all traces of precipitated gold from the sides and bottom. After sterilization they should be kept in a suitable dust-proof glass container until used. It is important to avoid contamination of the tubes by alkaline cleaning mixtures. Pipettes, rinsed in an automatic washer, are dried with alcohol and ether and sterilized in a pipette box. Confusing results will be avoided if a suitable supply of glassware is reserved solely for use in the test. *We are convinced that upon the care with which the cleaning and sterilization of glassware is carried out depends the success of the preparation of the gold solution and the reliability of the entire reaction.*

B. Solutions Required.

(1) *Distilled Water.*—The preparation of the distilled water is the most important stage in the making of colloidal gold solutions. Ordinary tap water and ordinary distilled water are both unsuited for preparing the reagent. Freshly distilled water, received in a sterile flask provided with a side glass connecting tube, is immediately redistilled and used within two or three hours; if allowed to stand much longer the water seems to acquire properties which render it unfit for use. No rubber stoppers or connections should be used in the distilling apparatus.

(2) *NaCl Solution* (0.4%).—This solution, made with doubly distilled water and Merck's "Blue Label" sodium chloride, keeps for a long time, but it is desirable to prepare it at least every two weeks. There seems to be no advantage in making this dilution each time from a stock 10% solution, as recommended by some authors. This particular strength is used because it causes no coagulation of colloidal gold. At the same time it is of sufficient concentration to hold globulins and nucleo-proteins in solution. Spinal fluids diluted with water exert no action upon a gold solution.

(3) *Colloidal Gold Solution.*—The ingredients required to prepare this indicator are:

a. Doubly distilled water.
b. Gold chloride crystals (yellow). } Merck's "Blue
c. Potassium carbonate. } Label" Reagents.
d. Formalin.

One litre of water is heated to 60° C. in a sterile Jena beaker. At this temperature 10 cc. each of a 1% aqueous solution of gold chloride and a 2% solution of potassium carbonate are added synchronously and thoroughly mixed at once. From this point the solution is heated as rapidly as possible, by using a four or

six flame Bunsen burner, until a temperature of about 90°C., but not exceeding 95° C., is reached. The flame is turned out, and while the contents of the beaker are briskly agitated, 10 cc. of a 1% aqueous solution of formalin are gradually added. The previously clear, colorless liquid at once undergoes a brilliant reaction, with reduction of the gold to a colloidal state, shown by the production of a beautiful play of colors. The resultant solution should meet the following criteria:

1. Color: A rich brilliant red with an orange glint when viewed in thin layers. The presence of any purple or blue shades must be avoided.

2. Such solutions must be absolutely clear and transparent when seen from any angle by any light. The existence of a superficial fluorescent layer is an indication for rejecting the reagent.

3. Boiling causes no change in the physical properties or reacting ability of good solutions.

4. They do not dialyse or diffuse.

5. Protected from evaporation, such solutions remain unchanged for an indefinite length of time, exposed to light and room temperature.

6. With normal spinal fluids, such solutions give no reaction, while with a paretic fluid complete *Ausflockung* occurs in the first 4 to 6 tubes.

Other methods for the standarization of gold solutions are greatly to be desired so that workers may always employ a comparable indicator. Occasionally, a solution meeting all of the first five requirements, will fail absolutely to react with a known abnormal spinal fluid: the cause for this is not known to us. We have tried other reducing agents, such as glucose and tannin, but with results inconsistent and generally unsatisfactory. It is useless to attempt to "doctor up" a solution which falls short of the first two requirements. Provided due care is exercised in the preparation of the water and the cleaning of the glassware, satisfactory colloidal solutions can always be obtained by the method above described.

C. The Cerebrospinal Fluid.

The lumbar puncture needles employed, preferably made of iridio-platinum, should not be boiled prior to use. They should be cleaned by drawing through them distilled water, alcohol and ether, after which they are sterilized in an ignition tube along with two small test tubes cleaned with the same reagents, as shown in Fig. 1. Every needle must be examined frequently and all traces of rust removed from its interior and stilette. If the pressure of the spinal fluid is to be determined, it must be done first, and after disconnecting the manometer, 10 or 15 drops of fluid are allowed to escape before any is collected for use. Fluids can be kept for at least several days before the test is carried out, though we have examined all specimens as soon as possible. Spinal fluids contaminated either with blood or bacteria are unfit for examination. Sterile fluids kept on ice for several weeks show practically no change in their reaction to solutions of colloidal gold.

Fig. 1. Sterile Lumbar Puncture Outfit.

3. Technique of the Test.

Place 11 sterile test tubes in a suitable rack. With a 10 cc. pipette measure 1.8 cc. of 0.4% salt solution into the first tube, and 1 cc. into each of the remaining. By means of a graduated 1 cc. pipette 0.2 cc. of spinal fluid are now added to the first tube and thoroughly mixed: it is to be noted that unless the contents of the pipette are completely expelled each time, an error in the dilution is introduced. Transfer 1 cc. of the 1-10 dilution of spinal fluid from the first to the second tube, where the mixing process is repeated and a 1-20 dilution results. In a similar manner dilutions are made in the remaining eight tubes, 10 dilutions in all, ranging from 1-10 to 1-5120. The 11th tube serves as a control to which no spinal fluid is added. It does not seem necessary to carry the dilutions higher, though in some isolated cases the reaction obviously would have gone beyond the 10th tube. After this dilution has been completed, 5 cc. of colloidal gold are added to each of the 11 tubes with a 25 cc. certified pipette. The reagent should be added and mixed as rapidly as possible; otherwise, reactions which are misleading and inaccurate will occur. The length of time required thus to examine a spinal fluid is approximately 5 minutes. While it is true that after some experience one may judge at once, with fair accuracy, of the degree of the reaction, it is best to wait 10 to 12 hours before making final readings. It has been our custom, therefore, to carry out the test late in the afternoon, reading the results the following morning, the tubes meanwhile standing at room temperature, and not necessarily stoppered. Reactions remain unchanged for at least 2 to 3 weeks, provided evaporation is guarded against and the tubes are kept in the ice-box. No attempt to record final readings with artificial light should be made, since this renders true color values extremely difficult to interpret.

4. The Reaction Observed.

This consists in color changes due to alterations in the dispersion value of the colloidal gold. A negative reaction may be represented by zero; the maximum precipitation, obtained with paretic fluids, consisting in complete decolorization, may be expressed conveniently by the figure 5. Between these two extremes, shades occur, running from pale blue through purple, violet, lilac and red-blue, to which numerical values have been assigned, as shown in Fig. 2. This diagram also indicates a method for the graphic representation of reactions. The regularity with which these color changes occur at certain maxima is quite striking. For this reason certain so-called characteristic reaction zones have been described. These are:

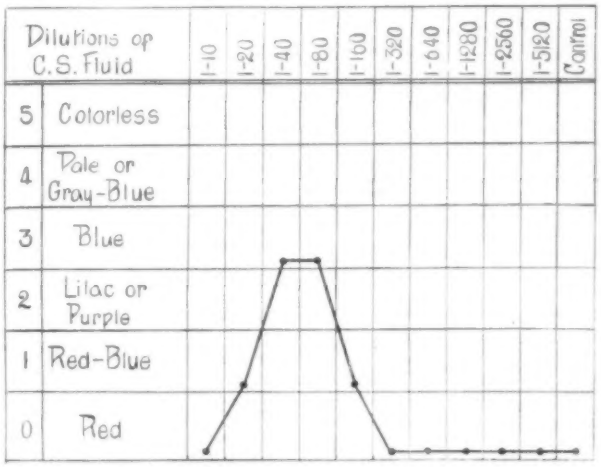

Fig. 2.—Diagram showing numerical values assigned to colors, and a reaction in the "luetic zone."

1. The "luetic zone" confined to the first 4 or 5 tubes. In this the precipitation is usually greatest in the dilutions 1-40 to 1-160 and never exceeds a "4" reaction.

2. The "meningitic zone" with *Verschiebung nach oben*, a phrase introduced by Lange. By this is meant a reaction maximum in the higher dilutions. Such a curve is represented in Fig. 3.

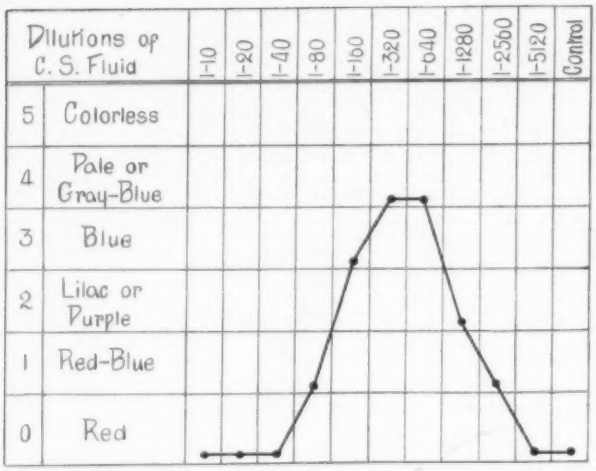

FIG. 3.—The reaction in meningitis with typical *Verschiebung nach oben.*

3. From observations herewith presented we feel that the curve in dementia paralytica is sufficiently constant to justify the introduction of the term "paretic zone." This zone comprises the first 3 to 6 tubes, in which the reaction is characteristically of the "5" type (Fig. 4).

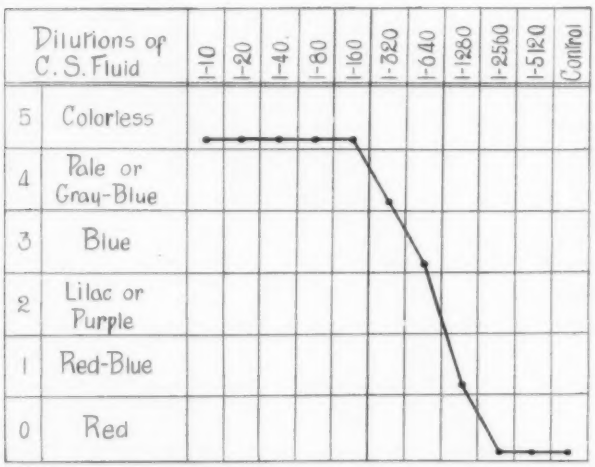

FIG. 4.—The characteristic curve of general paresis.

5. NATURE OF THE REACTION.

The exact nature of the reaction, it must be admitted, is not known. This is necessarily the case, since the exact combination and nature of the protein substances which may occur in the spinal fluid under normal or abnormal conditions, have not been determined. Lange is inclined to interpret the reaction as an indication of the occurrence of different qualitative mixtures of protein substances rather than of a true quantitative increase in one or other of the protein constituents. There is considerable evidence in favor of this view, since the strength of the reaction apparently bears no constant relation to the amount of protein present, as revealed by the ordinary tests. Other writers, as Zaloziecki,[14] are inclined to view it as an immunity reaction, more or less analogous to the "floccule reaction" of Porges and Meier,[15] Hermann and Perutz[16] and others, used as a diagnostic test for luetic conditions. Exponents of colloidal chemistry rather incline to the idea that the color changes are induced by variations in the dispersion value of one or more colloidal substances present in the spinal fluid. No attempt has been made by us to prove which, if any, of these theories is correct, but merely to determine whether or not the test is of sufficient value to warrant its adoption as an aid to clinical diagnosis.

6. ROUTINE FOLLOWED.

The present report is based upon the examination of 210 spinal fluids secured from 171 cases.*

All fluids have been subjected to the following routine examination: *First,* a quantitative estimation of the cells has been made as soon after withdrawal of the fluid as possible, usually within ten or fifteen minutes. We have used a diluting solution consisting of distilled water, 50 cc.; glacial acetic acid, 2 cc.; and methyl violet, 0.1 of a gram. This stains the nuclei of the cells with sufficient clearness to permit of a fairly accurate differential count at the same time that the quantitative estimation is made. In all instances counts have been made with the Fuchs-Rosenthal counting chamber. *Second,* increase in the protein content has been tested for by the Ross-Jones method. In our experience this test has yielded results which are both trustworthy and easily obtained. *Third,* the Wassermann reaction has been carried out by one of us on all spinal fluids and on specimens of blood from the same patients when available. Every fluid and serum has been tested with at least two, and in many instances with three, antigens, namely, a plain alcoholic extract of the human heart, a similar extract, strengthened by the addition of .4% cholesterin, and an alcoholic extract of syphilitic liver. It should be noted in passing, that in the great majority of the cases the results obtained with these three antigens have been parallel. There have been, however, undoubted cases of syphilitic infection in which the cholesterinized antigen alone has given a positive result, the other two antigens yielding an absolutely negative or, at most, a 1 + inhibition. Such cases are indicated in the reports given below. *Fourth,* the colloidal gold reaction.

7. TABULATION OF RESULTS.

Detailed case reports are herewith presented. The numbers 1-10 under Gold Reaction refer to the dilutions previously described. A star indicates that the fluid was sent from an outside source. Wassermann reactions positive with a cholesterin antigen only are indicated by the letter C. A cell count of ten or over has been regarded as a pleocytosis.

* The rapidity with which we have been able to secure this number of observations is due in large part to the hearty co-operation received from the various members of the medical, pediatrical and dispensary staffs of this hospital, to whom we express our greatest appreciation. It is also a pleasure to acknowledge the receipt of numerous spinal fluids from the Manhattan State Hospital, through the kindness of Dr. Cheney; from the Central Islip Hospital, Long Island, through Dr. Wescott's help; and from the City Detention Hospital at Bay View, through the co-operation of Dr. Kenneth B. Jones.

TABLE I. MISCELLANEOUS GROUP.

Case No.	W. R. Blood.	Cerebro-spinal fluid. W. R.	Cells.	Globulin.	Gold reaction. 1 2 3 4 5 6 7 8 9 10	Remarks.
A. (2)	Not done.	Negative.	1	Negative.	0 0 0 0 0 0 0 0 0 0	Pneumonia; meningismus.
B.B. (3)	Negative.	....do....	1	....do....	0 0 0 0 0 0 0 0 0 0	Multiple sclerosis.
N.B. (4)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Hysteria; epileptiform attacks.
Do. (6)	....do....	....do....	10	....do....	0 0 0 0 0 0 0 0 0 0	Epileptiform attacks.
Di. (6)	....do....	....do....	27	....do....	0 0 0 0 0 0 0 0 0 0	Acute mania.
B. (8)	....do....	Not done.	1	.....	2 3 3 2 1 0 0 0 0	Brain tumor.
B. (9)	....do....	Negative.	800	Positive..	4 4 5 5 5 5 5 2 1 0	Cells mixed type.
			1184	....do....	5 5 5 5 5 5 5 4 3 2	
			210	....do..	5 5 5 5 5 4 2 1 0 0	Brain abscess.
B. (10)	....do....	....do....	1	Negative.	0 0 0 0 0 0 0 0 0 0	Neurasthenia.
C. (11)	....do..	....do....	1	....do....	0 0 0 0 0 0 0 0 0 0	Migraine.
C. (13)	....do....	....do....	0	....do....	0 0 0 0 0 0 0 0 0 0	Manic depressive psychosis.
C. (19)	....do....	C. Positive..	2	Faintly +	0 0 0 0 0 0 0 0 0 0	Chronic nephritis; uraemia.
I. (24)	....do....	Negative.	6	Faintly +	0 0 0 0 0 0 0 0 0 0	Anxiety neurosis.
D. (130)	....do....	....do....	2	Negative.	0 0 0 0 0 0 0 0 0 0	Dermatitis herpetiformis.
D. (25)	....do....	....do....	5	....do....	1 2 3 3 1 0 0 0 0	Typhoid fever; patient extremely toxic
F. (129)	Not done.	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Oxycephaly.
F. (135)	Negative.	....do....	4	....do....	0 0 0 0 0 0 0 0 0 0	Septicaemia.
G. (35)	....do....	....do....	1	....do....	0 0 0 0 0 0 0 0 0 0	Varicella.
H. (43)	Not done.	....do....	34	Positive..	0 0 0 0 0 0 0 0 0 0	Alimentary intoxication.
H. (46)	Negative.	....do....	4	Faintly positive.	1 1 1 2 3 2 0 0 0 0	Manic-depressive insanity.
J. (51)	....do....	....do....	2	Negative.	0 0 0 0 0 0 0 0 0 0	Chronic encephalitis; operation.
J. (52)	....do..	....do....	5	....do....	0 1 1 2 1 0 0 0 0	Tumor of spinal cord; compression.
J. (53)	....do....	....do....	2	Positive..	1 1 2 2 2 0 0 0 0	Psychoneurosis (?).
K. (59)	....do....	....do....	9	Negative.	0 0 0 0 0 0 0 0 0 0	Acidosis; autopsy.
K. (156)	....do....	....do....	4	....do....	0 0 0 0 0 0 0 0 0 0	Copaiba rash.
K. (62)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Psychoneurosis.
L. (63)	....do....	....do....	4	....do..	0 0 0 0 0 0 0 0 0 0	Serous meningitis.
L. (64)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Psoriasis.
L. (66)	Not done.	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Eczema.
L. (68)	Negative.	....do....	5	....do....	1 2 2 1 0 0 0 0 0	Positive history of lues. Cerebral sclerosis: convulsions.
M. (71)	....do....	....do....	3	....do....	0 0 0 6 0 0 0 0 0	Acnitis.
M. (72)	....do....	....do....	2	....do....	0 1 2 3 1 0 0 0 0	Dementia praecox; luetic history.
M. (73)	....do....	....do....	4	....do....	0 0 0 0 0 0 0 0 0 0	Pulm. tuberculosis.
M. (74)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Psychoneurosis.
M. (76)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Chronic nephritis.
M. (77)	....do....	....do....	6	....do....	0 0 0 9 0 0 0 0 0	Pneumonia; meningismus.
M. (78)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0	Psychoneurosis.
M. (79)	....do....	C. Positive..	3	....do....	1 1 2 3 2 1 0 0 0	Cerebellar tumor (?).
M. (80)	....do....	Negative.	5	....do....	0 0 0 0 0 0 0 0 0	Hydrocephalus.
M. (81)	....do....	C. Positive..	17	Positive.	1 1 2 2 1 0 0 0 0	Lead encephalopathy.
N. (84)	....do....	Negative.	0	Negative.	0 0 0 0 0 0 0 0 0	Syphilophobia.
P. (133)	....do....	....do....	3	....do....	0 0 0 0 0 0 0 0 0	Hysteria.
P. (88)	....do....	....do....	3	....do....	0 0 0 0 0 0 0 0 0	Psoriasis.
R. (92)	....do....	....do....	5	....do....	0 0 2 3 1 0 0 0 0	Cystic glioma; luetic history.
R. (93)	....do....	....do....	12	....do....	0 0 0 0 0 0 0 0 0	Neurasthenia.
R. (95)	....do....	....do....	1	....do....	1 2 2 1 0 0 0 0 0	Psychoneurosis. Tabes (?).
R. (97)	....do....	....do....	8	....do....	0 3 0 0 0 0 0 0 0	Chronic meningitis (?).
S. (131)	....do....	....do....	9	....do....	0 4 0 0 0 0 0 0 0	Cerebral sclerosis.

TABLE I. MISCELLANEOUS GROUP.—Continued.

Case No.	W. R. Blood.	Cerebro-spinal fluid. W. R.	Cells.	Globulin.	Gold reaction. 1 2 3 4 5 6 7 8 9 10	Remarks.
S. (105)	Negative.	Negative.	9	Positive .	1 1 1 1 2 3 3 1 1 0	Cerebral sclerosis. Xanthochromia.
S. (134)	....do....	....do....	3	....do....	0 0 0 0 0 0 0 0 0 0	Compression of spinal cord.
S. (106)	Not done.	....do....	2	Negative.	0 0 0 0 0 0 0 0 0 0	Malnutrition.
S. (157)	Negative.	....do....	0	....do....	0 0 0 0 0 0 0 0 0 0	Cerebral arterio-sclerosis.
S. (108)	....do....	....do....	3	....do....	3 3 2 2 2 1 0 0 0	Septicaemia; fluid contains bile.
T. (110)	....do....	....do....	2	....do....	0 0 0 0 0 0 0 0 0 0	Normal child.
T. (150)	....do....	....do....	1	....do....	0 0 0 0 0 0 0 0 0 0	Chronic nephritis.
V. (115)	....do....	....do ...	2	....do....	1 1 2 1 0 0 0 0 0	Aran-Duchenne type progressive central muscular atrophy.
W. (117)	....do....	....do....	0	....do....	0 0 0 0 0 0 0 0 0 0	Pernicious anaemia.
W. (118)	....do....	C. Positive .	15	....do....	1 1 2 2 1 0 0 0 0	Diabetes insipidus; chancre 1 yr. ago.
W. (123)	....do....	Negative.	4	....do....	0 0 0 0 0 0 0 0 0	Hysteria.
W. (126)	Not done.	....do....	470	....do....	0 0 0 0 0 0 0 0 0	Mumps, complicating meningitis.
L. (161)	Negative.	....do....	3	....do....	0 0 0 0 0 0 0 0 0	Post typhoid psychosis.

TABLE II. PURULENT MENINGITIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid. W. R.	Cells.	Globulin.	Gold reaction. 1 2 3 4 5 6 7 8 9 10	Remarks.
C. (12)	Not done.	Negative.	†	Positive ...	4 4 4 4 1 2 3 3 3 2	Pink tinge in first 5 tubes.
					5 5 5 5 4 3 4 4 3 0	
E. (29)	....do....	....do....	†	....do.....	1 1 1 2 2 3 2 1 1 1	
					1 1 1 1 2 3 3 3 2 1	
F. (30)	....do....	....do....	†	....do.....	1 1 2 2 3 3 3 2 1 0	Daily administration of meningococcus serum.
					0 0 0 0 2 3 3 3 1 0	
					0 0 0 1 2 3 2 1 1 0	
					1 1 1 2 3 3 2 1 0 0	Diplococci present at last examination.
					1 1 1 2 3 3 2 1 0 0	
					5 5 5 4 3 2 0 0 0 0	Epidemic meningitis.
T. (114)	.....do....	....do....	†	....do	2 2 3 3 3 4 4 4 3 1	Aortic aneurysm. Autopsy.

† Countless pus cells.

TABLE III. TUBERCULOUS MENINGITIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid. W. R.	Cells.	Globulin.	Gold reaction. 1 2 3 4 5 6 7 8 9 10	Remarks.
C. (15)	Negative.	Negative.	180	Positive.....	2 2 2 3 4 4 2 1 0 0	Tubercle bacilli found in C.S.F.
C. (17)	Not done.	....do....	142	.....do.....	1 1 1 2 3 3 0 0 0 0	Autopsy.
F. (31)	.....do....	....do....	3000	.....do.....	0 0 0 1 3 4 4 2 1 0	Autopsy. Fluid removed post mortem.
H. (41)	Negative.	....do....	135	.....do.....	2 3 3 1 1 0 0 0 0 0	Bacilli demonstrated.
H. (48)	Not done.	....do....	234	.....do.....	0 0 0 0 1 3 2 1 0 0	Do.
			157	.....do.....	0 0 0 0 0 1 2 1 0 0	
P. (86)	Positive..	Positive..	86	.....do.....	0 0 0 2 3 3 2 1 0 0	Bacilli demonstrated. Congenital lues ? symptoms.
T. (109)	Negative.	Negative.	120	.....do.....	0 1 1 2 2 2 1 0 0 0	Bacilli demonstrated. Autopsy.
			88	.....do.....	0 1 1 2 2 1 0 0 0 0	
			112	.....do.....	1 1 2 2 1 1 0 0 0 0	
			122	.....do.....	1 1 2 3 3 2 1 0 0 0	

TABLE IV. CONGENITAL LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
B. (7)....	Positive..	Negative.	4	Positive..	1	2	3	3	2	1	0	0	0	5	injections Neosalvarsan.
C. (14)...	....do....	....do....	14	....do....	1	1	2	3	3	1	1	0	0	2	injections Neosalvarsan.
C. (20)...	....do....	Positive..	4	....do....	2	3	3	2	1	0	0	0	0		Spastic paraplegia.
C. (23)...	....do....	Negative.	23	....do....	1	2	2	2	2	0	0	0	0		
H. (140)..	....do....	....do....	1	Negative.	0	0	0	0	0	0	0	0	0		
M. (70)...	....do....	....do....	1	Positive..	2	3	3	2	1	1	0	0	0		Mongoloid idiot.
S. (101)..	....do....	....do....	2	Negative.	1	2	3	3	1	0	0	0	0		
S. (103)..	....do....	....do....	1	....do....	0	1	2	2	1	0	0	0	0		
S. (104)..	....do....	....do....	21	....do....	0	0	0	0	0	0	0	0	0		
Y. (127)..	....do....	....do....	3	....do....	1	2	2	1	0	0	0	0	0		

† Not done.

TABLE V. SECONDARY LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
Pr. (151).	Positive..	Negative.	11	Faintly +	0	0	0	0	0	0	0	0	0		Condylomata.
F. (32)...	....do....	....do....	3	Negative.	0	0	1	2	1	0	0	0	0		Mucous patches; bone pains.
J. (56) ...	....do....	....do....	13	Positive .	2	3	3	2	1	0	0	0	0		Mucous patches; alopoecia; papular eruption.
P. (85)...	....do....	....do....	2	Negative.	1	1	2	1	1	0	0	0	0		Papular eruption.
W. (125).	....do....	....do....	32	....do ...	0	1	2	2	1	0	0	0	0		Mucous patches.

TABLE VI. TERTIARY LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
J. A. (153)	Positive..	Negative.	2	Negative.	0	0	0	0	0	0	0	0	0	0	Syphilitic mesaortitis.
C. (16)...	....do....	....do ...	0	....do ...	2	3	3	3	2	1	0	0	0		Lues not suspected.
F. (33)...	....do....	....do....	2	....do ...	0	0	0	0	0	0	0	0	0		Aortic aneurysm.
G. (37)...	....do....	....do....	1	....do ...	2	3	3	2	1	0	0	0	0		Gumma of palate
H. (12)...	Negative.	....do....	3	....do ...	0	0	0	0	0	0	0	0	0		Treated several years.
H. (14)...	Positive..	....do....	5	....do....	0	0	0	0	0	0	0	0	0		Latent case.
H. (19)...	Negative.	....do....	5	....do....	1	2	2	1	0	0	0	0	0		Thorough treatment.
J. (155)..	Positive..	Positive..	5	....do....	0	0	0	0	0	0	0	0	0		Aortic aneurysm.
K. (30)...	....do....	Negative.	2	....do....	0	0	0	0	0	0	0	0	0		
M. (83)...	....do....	....do....	1	....do....	0	1	3	2	1	0	0	0	0		Aortic aneurysm
W. (120)..	....do....	....do....	3	....do....	0	0	0	0	0	0	0	0	0		Autopsy: mesaortitis.

TABLE VII. TABES DORSALIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
H. (40)...	Positive..	Positive..	135	Positive.	1	1	2	3	3	1	0	0	0		
H. (50)...	Negative.	C. Positive..	94	....do...	5	5	5	5	4	1	0	0	0	1	intravenous dose of "606" between examinations.
					1	1	2	1	0	0	0	0	0		
J. (55)...	Positive..	Positive..	38	....do....	1	1	2	3	3	1	1	0	0		Intra-spinous treatment.
K. (61)...	....do....	Negative.	3	....do....	1	1	2	2	2	0	0	0	0		
L. (65)...	....do....	Positive..	35	....do....	1	1	2	3	2	1	0	0	0		
M_2 (82)...	Negative.	....do....	1	Negative.	3	3	3	2	1	0	0	0	0		Treated case.
P. (89)...	....do....	Negative.	4	....do....	1	1	2	2	1	0	0	0	0		Extensive treatment.
			4	....do....	0	0	0	0	0	0	0	0	0		
P. (99)...	Positive..	Positive..	9	Positive..	1	1	3	3	2	1	0	0	0		
R. (94)...	Negative.	Negative.	5	Negative.	1	1	2	3	3	1	0	0	0		Treated since 1899.
W. (124) .	Positive..	Positive..	11	Positive..	3	3	4	4	3	2	0	0	0	1	intravenous injection of "606" between examinations
			7	....do....	0	0	1	1	0	0	0	0	0		

TABLE VIII. CEREBRO-SPINAL LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
D. (6)....	Positive..	Negative.	6	Faintly positive.	0	1	3	2	1	0	0	0	0		
C. (21)...	Weak positive.	....do ...	2	Positive..	2	2	3	3	3	3	2	1	0	0	Vigorous specific therapy.
D. (26)...	Positive..	....do....	5	Negative.	0	0	0	0	0	0	0	0	0	0	.6 salvarsan previously.
F. (152)..	....do....	Positive..	48	Positive..	3	3	4	3	1	0	0	0	0		Congenital syphilis.
*F. (34)..	Not done.	....do....	†	....do....	0	1	3	4	4	3	1	0	0		
H. (47)...	Positive..	....do ...	50	....do....	3	4	4	4	3	1	0	0	0		Congenital case.
L. (67)...	Negative.	Negative.	3	Faintly positive.	1	1	2	1	0	0	0	0	0		Optic atrophy; luetic history.
M. (75)...	Positive..	Positive..	35	Positive..	1	2	2	1	0	0	0	0	0		Bilateral abducens palsy.
Q. (91)...	....do....	Negative.	7	Negative.	0	0	1	2	1	0	0	0	0		Hemiplegia; treated case.
R. (96)...	....do....	Positive..	13	Positive..	4	4	4	0	0	0	0	0	0		Intra-spinous treatment.
			8		5	4	4	4	3	2	1	0	0		
R. (98)...	....do....	Negative.	2	Negative.	0	0	0	0	0	0	0	0	0		Epileptiform attacks.
R. (99)...	Negative.	....do....	27	Positive..	0	0	1	2	1	0	0	0	0		Intensive "606" therapy; spastic paraplegia.
T. (113)..	Positive..	Positive..	167	....do....	1	2	4	3	2	0	0	0	0		Luetic aortitis. No nervous system symptoms.
V. (137)..	....do ...	....do ...	9	....do....	4	4	3	3	1	0	0	0	0		Advanced case.
*W. (144).	....do....	....do....	15	....do....	1	2	3	1	0	0	0	0	0		

† Increased.

TABLE IX. GENERAL PARESIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
T. (5)....	Positive..	Positive..	57	Positive..	5	5	5	5	5	5	4	2	1	0	
F. (5)....	....do....	....do....	27	....do....	5	5	5	5	4	3	1	0	0	0	
M. (5)....	....do....	....do....	39	....do....	5	5	5	5	4	3	1	0	0	0	
Ba. (5)...	....do....	....do....	12	....do....	5	5	5	5	3	2	1	0	0	0	
Be. (5)...	....do....	....do....	13	....do....	5	5	5	5	5	4	3	2	0	0	
Tr. (5)...	....do....	....do....	178	....do....	5	5	5	5	5	4	2	1	0	0	
P. (5)....	....do....	....do....	26	....do....	5	5	5	5	5	5	4	2	1	0	
H. (5)....	....do....	....do....	118	....do....	5	5	5	5	5	5	4	2	0	0	
G. (6)....	....do....	....do....	2	Weakly positive.	5	5	5	4	3	1	0	0	0		
B. (6)....	....do....	....do....	6	Positive..	5	5	5	5	5	4	1	0	0	0	
O. (6)....	....do....	....do....	3	....do....	5	5	5	4	3	1	0	0	0		
W. (151).	....do....	....do....	16	....do....	5	5	5	4	3	1	0	0	0		

TABLE IX. GENERAL PARESIS.—Continued.

Case No.	W. R. Blood.	Cerebro-spinal fluid. W. R.	Cells.	Globulin.	Gold reaction. 1	2	3	4	5	6	7	8	9	10	Remarks.
S. (151)..	Positive..	Positive .	34	Positive .	5	5	5	5	4	3	1	0	0		
T. (151)..	....do....	....do....	53	....do....	5	5	5	4	3	1	0	0	0		
*B. (132).	....do....	....do....	+	....do....	5	5	5	5	5	4	2	1	0		
*C. (18)..	....do....	....do....	+	....do....	5	5	5	5	5	5	4	1	0		
*D. (141).	Not done.	....do....	23	....do....	5	5	5	4	1	0	0	0	0		
D. (27)...	Negative.	....do....	26	....do....	5	5	4	3	2	1	0	0	0	4	intravenous and intra-spinous treatments. Tabo-paresis.
			24	....do....	5	5	5	5	4	3	1	0	0		
			7	....do....	5	5	5	4	3	1	0	0	0		
*F (145)..	Not done.	....do....	53	....do....	5	5	5	5	4	2	1	0	0		
*G. (148).	....do....	....do....	138	....do....	5	5	5	5	5	4	1	0	0		Tabo-paresis.
G. (154)..	Positive..	....do....	37	....do....	5	5	5	5	5	4	1	0	0		
G. (36)...	....do....	....do....	40	....do....	5	5	5	5	5	5	4	3	2		Advanced case.
*G. (143).	....do....	....do....	42	....do....	5	5	5	5	4	2	1	0	0		
G. (38)...	....do....	....do....	+	....do....	5	5	5	5	5	5	4	3	1		Advanced case.
H. (139)..	....do....	....do....	108	....do....	5	5	5	5	3	2	1	0	0		
H. (45)...	....do....	....do....	7	....do....	5	5	5	5	2	2	1	1	0		
			12	....do....	5	5	5	5	4	3	2	0	0		Intra-spinous treatment. No clinical improvement
			10	....do....	3	3	3	3	2	1	0	0	0		
			13	....do....	2	2	3	3	2	1	0	0	0		
J. (51)...	Positive .	....do....	28	....do....	5	5	5	5	5	4	2	1	0		
J. (57)...	Negative.	Negative.	121	....do....	5	5	5	4	3	2	1	0	0		W. R. negative repeatedly.
K. (58)...	....do....	Positive .	3	....do....	5	5	5	5	5	4	3	2	0		Blood W. R. positive 5 months previously. Treated case.
L. (147)..	Positive .	....do....	24	....do....	5	5	5	5	3	1	0	0	0		
*L. (138).	Not done.	....do....	+	....do....	5	5	5	4	3	1	0	0	0		
*L. (160).	....do....	....do....	+	....do....	5	5	5	5	5	4	2	1	0		
*L. (158).	Positive .	....do....	+	....do....	5	5	5	5	4	2	1	0	0		
M. (69)...	....do....	....do....	43	..do....	5	5	5	4	3	2	1	0	0		Juvenile paresis; age 5 yrs.
M. (146).	....do....	....do....	72	....do....	5	5	5	5	5	4	1	0	0		
P. (87)...	....do....	....do....	3	....do....	5	4	4	4	2	1	0	0	0		Intra-spinous therapy.
			9	....do....	2	2	3	4	3	2	0	0	0		
S. (102)..	....do....	....do....	8	....do....	5	5	5	5	4	4	3	1	0		Intra-spinous therapy. No clinical improvement. An advanced case.
			12	....do....	5	5	5	5	5	4	3	1	0		
			7	....do....	5	5	5	5	4	3	2	1	0		
			14	....do....	5	5	5	4	3	1	0	0	0		
*S. (142).	Not done.	....do....	11	....do....	5	5	5	4	2	1	0	0	0		Intra-spinous therapy.
S. (107)..	Positive .	....do....	22	....do....	5	5	5	5	5	4	2	0	0		Intra-spinous therapy.
			27	....do....	5	5	5	4	3	2	1	0	0		
			4	....do....	5	5	5	5	4	2	0	0			
T. (111)..	....do....	....do....	23	....do....	5	5	5	4	2	1	0	0	0		Intra-spinous treatment.
			5	....do....	5	5	5	5	2	1	0	0	0		
			4	....do....	5	5	5	4	2	1	0	0	0		
T. (112)..	....do....	....do....	+	....do....	5	5	5	5	4	4	1	0	0		
V. (116)..	....do....	....do....	30	....do....	5	5	5	5	4	3	2	1	0		Much intra-spinous therapy. No clinical improvement.
			25	....do....	5	5	5	5	5	4	2	0	0		
			14	....do....	5	5	5	4	2	1	0	0	0		
			11	....do....	5	5	5	4	3	1	0	0	0		
W. (119).	Weakly positive.	....do....	17	....do....	5	5	5	5	4	1	0	0	0		Much treatment, with clinical improvement.
			20	....do....	5	5	5	4	3	1	0	0	0		
			8	....do....	5	5	5	3	1	0	0	0	0		
W. (139).	Positive .	....do....	62	....do....	5	5	5	5	4	2	1	0	0		
*W. (121)	....do....	....do....	+	....do....	5	5	5	5	5	4	1	0	0		
W. (122).	Negative.	....do....	8	....do....	5	5	5	4	4	3	1	0	0		Extensive treatment; marked clinical improvement.
			5	....do....	5	5	5	4	3	1	1	0	0		
			6	....do....	3	4	4	3	1	0	0	0	0		
			5	....do....	1	1	2	1	0	0	0	0	0		
W. (136).	Positive.	....do....	22	....do....	5	5	5	5	4	3	1	0	0		
Z. (128)..	....do....	....do....	44	....do....	5	5	5	5	4	2	0	0	0		Tabo-paresis; intra-spinous treatment.
			10	....do....	5	5	5	4	3	2	1	0	0		
			9	....do....	5	5	5	3	1	0	0	0	0		
			9	....do....	5	5	4	2	1	0	0	0	0		
A. (1)....	....do....	Negative.	4	....do....	5	5	5	4	3	2	2	1	0		Intra-spinous treatment.

*+ Increased.

TABLE X. COMPOSITE TABLE OF RESULTS.

Condition.	Number of cases.	Blood. Wassermann. Positive.	Blood. Wassermann. Negative.	Cerebro-spinal fluid. Wassermann. Positive.	Cerebro-spinal fluid. Wassermann. Negative.	Phase I. Positive.	Pleocytosis.	Gold reaction. Positive.	Gold reaction. Negative.	Gold reaction. Reaction zone.
Miscellaneous group.	60	0	60	C. 4	56	6	8	16	44	Variable, most in lower dilutions.
Purulent meningitis.	4	Not done		.....	4	4	4	4	0	*Verschiebung nach oben.*
Tuberculous meningitis.	7	1	6	1	6	7	7	7	0	Upper dilutions; inconstant.
Congenital lues....	10	10	0	1	9	5	3	8	2	Luetic zone.
Secondary lues.....	5	5	0	0	5	1	3	4	1	Do.
Tertiary lues.....	11	9	2	C. 1	10	0	0	4	7	Do.
Tabes.....	10	6	4	7	3	7	5	10	0	Do.
Cerebro-spinal lues	15	12	3	8	7	12	8	13	2	Do.
General paresis....	49	39	4 (6 not done)	47	2	49	43	49	0	Paretic zone.

8. Analysis of Results.

A. Miscellaneous Group.

Most of these cases were punctured with the expectation of finding normal spinal fluid. Seventy-five per cent of them caused no gold precipitation. Where reactions occurred, pathological conditions, presumably sufficient to account for them, were present in a large majority, as may be seen by reference to the detailed reports.

B. Purulent Meningitis.

In two of eight examinations made upon four cases, typical *Verschiebung nach oben* was observed. Two gave reactions analogous to the paretic type, with the noteworthy differences that the supernatant fluid in the low dilutions showed a pink turbidity and the precipitation continued throughout the remaining tubes.

The anomalous result observed in Case F 30 followed repeated injections of antimeningococcus serum.

C. Tuberculous Meningitis.

Eleven cases, confirmed either by the finding of tubercle bacilli or by autopsy, gave, with one exception, maximum color changes in the higher dilutions. One observation confirms Eicke's[17] statement that in the early stages the reaction may simulate that of syphilis. As the disease advances there is *Verschiebung nach oben.*

D. Congenital Syphilis.

Of ten cases, three showed moderate pleocytosis, five a positive Phase I. Reactions of the luetic type were obtained in eighty per cent.

It is stated by Grulee and Moody[18] that "the Wassermann reaction and other laboratory tests as applied to the diagnosis of congenital syphilis are entirely inadequate, especially in very young infants." In the children's clinic of this hospital, experience has not borne out this statement. Except in the first few days of life, a positive Wassermann reaction can be

demonstrated in the blood in practically every instance, and was present in one hundred per cent of the cases constituting the present series.

E. Secondary Syphilis.

Reactions in the "luetic zone" occurred in four out of five cases. Eicke reports positive results in 60 of 136 examinations, at times even in the absence of pleocytosis and Phase I. This tends to support the view that syphilis, even in its early stages, is an exceedingly diffuse process, and emphasizes the importance of repeated lumbar punctures on all syphilities, in the hope of detecting the earliest manifestations of metaluetic disease.

F. Tertiary Syphilis.

In eleven cases, comprising instances of latent syphilis, gummatous lesions and vascular manifestations, a reaction in the luetic zone occurred in four. In none was there any demonstrable clinical evidence of central nervous system involvement. Several of the individuals were elderly men, who had had their primary infection many years before, and who, in all probability, will never develop cerebrospinal syphilis, tabes or paresis.

G. Tabes Dorsalis.

All showed luetic curves. With three exceptions, these were of moderate intensity, yet definite. This is contrary to the statement of Kaplan and McClelland,[19] who find in this group either no reaction at all or at most a very weak one in the first three tubes.

Though clinically a tabetic, Case H 50 may well be in an early stage of tabo-paresis, in which cases we have always found a reaction of the paretic type. In two instances, striking changes in the curves followed minimal amounts of therapy.

H. Cerebrospinal Syphilis.

Thirteen of the fifteen fluids examined reacted in the luetic zone, six with fairly marked intensity.

Eicke, and Jaeger and Goldstein[20] state that the reaction in cerebrospinal lues may simulate that of paresis, differing from the latter in that it appears only after standing for several hours. We have had no difficulty in differentiating the reactions in these two groups of cases.

I. General Paresis.

The series exhibits a striking uniformity of results, in that all of the 49 cases gave characteristic paretic curves.

The more advanced cases clinically have shown the most striking tests. M. 69, aged 5, a case of juvenile paresis, gave a typical reaction. That the reaction tends to remain unchanged both during remissions and after intensive intraspinous therapy, is in harmony with the "Wassermann fast" condition of the blood and spinal fluid observed in most instances of this disease. W. 122 alone has shown a marked diminution in the intensity of the gold reaction coincident with outspoken clinical improvement.

9. Summary and Conclusions.

1. The colloidal gold test is essentially a laboratory method. It can be performed rapidly and with a minimal amount of spinal fluid.

2. Extreme care in the preparation of reagents and the cleaning of glassware is imperative.

3. Normal fluids give negative reactions.

4. The test is of no aid in the diagnosis of purulent or tuberculous meningitis.

5. It has no advantage over known laboratory procedures in the diagnosis of congenital syphilis.

6. Reactions in secondary and tertiary syphilis are inconstant. Their significance when present is not known. The statement that they indicate the earliest stages of central nervous system involvement lacks proof.

7. The positive reactions observed in the majority of cases of tabes and cerebrospinal syphilis are not characteristic.

8. We feel that the reaction peculiar to paresis is sufficiently constant to warrant its use as an aid in the differentiation of this condition from others with which it might be confused.

9. It is possible that the test may prove to be more sensitive, than are those at present employed, as an indicator of the results of specific therapy in syphilitic diseases of the central nervous system.

10. Much may be expected from the application of colloidal chemistry to the study of biological problems.

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THE ESSENTIAL FEATURES OF ACIDOSIS AND THEIR OCCURRENCE IN CHRONIC RENAL DISEASE.

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OUTLINE.

I. General Discussion of Acidosis:
   1. Misuse of the term in the sense of free acid in the blood.
   2. Impoverishment of the body in fixed bases as a basis of the definition of acidosis.

II. Evidence of Acidosis in Renal Disease:
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   2. Diminution of carbon dioxide in the alveolar air.
   3. Changes in the body fluids:
      a. Increase in the acidity of the urine.
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   1. Determination of carbon dioxide content of the blood.
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   1. Decrease in the carbon dioxide of the blood.
   2. Decrease in the titratable alkalinity of the blood serum.
   3. Increase in the tolerance to fixed bases.
   4. Unreliability of the ammonia excretion as a criterion of acidosis.
   5. General methods of detecting acidosis.

V. Clinical Significance of Acidosis in Renal Disease with Reference to:
   1. Symptoms of uræmia.
   2. Diagnosis of uræmia.
   3. Estimation of degree of acidosis.
   4. Relation to salt action and to therapy.
   5. Considerations of the etiology of the acidosis.

The symptomatology of the commoner types of cardiorenal disease is comparatively well understood as far as the interpretation of the physical signs and symptoms is concerned. In the stage of uræmia, however, a characteristic dyspnœa occurs which has not been fully explained. In a typical case one sees very deep respirations, a tendency to prolonged expiration, and an increase in rate. This is accompanied either by a bright color of the mucous membranes or by a degree of cyanosis so slight that it is wholly out of proportion to the degree of dyspnœa. Similarly, the lungs upon physical examination show nothing to account for the dyspnœa. Such patients soon become drowsy and coma develops eventually. This description represents a classical case in a relatively pure type of renal disease. Such a picture is usually modified more or less extensively by complicating cardiac or pulmonary conditions. This type of dyspnœa is usually described under the term "renal asthma" or "air hunger." The latter term differentiates it more sharply from "cardiac asthma" and suggests also that the explanation may be the same as in the air hunger of diabetic coma in the sense that it is a dyspnœa due to acidosis. If an acidosis is present during the stage of uræmia, it would explain this dyspnœa very satisfactorily and would also have a fundamental bearing upon the question of therapy in renal disease, especially in regard to the use of neutral salts and alkalies. This paper will consider the explanation of the air hunger occurring in uræmia and the events leading up to the development of this symptom.

GENERAL CONSIDERATIONS IN REGARD TO ACIDOSIS.

The question of acidosis is one of the obscure factors in the chemical pathology of renal diseases. Inasmuch as the theory of acidosis is only in its developmental stage, there are naturally many obstacles in determining whether acidosis develops in the course of nephritis. Consequently, before taking up the discussion of the nephropathies, it is necessary, to analyze and define the fundamental characteristics of acidosis.

Perhaps the one greatest obstacle to the general acceptance of the theory of acidosis consists in a tendency to misinterpret the action of acids in the body. Both in American and in European literature one frequently sees the expression "free acids in the blood" and carbonates administered for the relief of acidosis have been spoken of as neutralizing "acids in the blood," the *freie Säure in dem Blut* of the German literature. In recent years the term "acidæmia" even has been introduced into the literature.

However, it is clearly established that death from acidosis is due to a deprivation of fixed bases. Walter[1] in 1877 showed that the blood in fatal experimental acidosis retained its alkaline reaction toward indicators such as litmus. Benedict[2] found that the concentration of hydrogen ions in the blood in advanced diabetic acidosis was not materially altered. The therapeutic benefit of the administration of bicarbonate is due to the replacement of carbonates which have been lost and not to the neutralization of any acids circulating in the body. The symptoms accompanying an acidosis are due, not to the presence of free acid in the blood, but to the lack of carbonates and the relief of these symptoms is due to the injected carbonates functioning as such in the blood. Subsequently, they may be neutralized by acid. Furthermore, it is evident that acid may become available more or less rapidly, even within a few hours according to the etiology of the acidosis, for the neutralization of large amounts of alkali. It is clear, however, that the carbonates, upon introduction into the body, do not meet with preformed acid in the circulating blood, for death takes place while the blood still contains alkalies or

alkali-yielding substances. The essential feature of the definition of acidosis has been stated clearly by Naunyn[3] under the term *hypalkalität*, by Emerson,[4] who uses the term "alkali starvation," and Palmer and Henderson,[5] who use the term "depletion of bicarbonate from the blood." It would seem necessary, however, to include other tissues, as well as the blood, since, in the absence of evidence to the contrary, it must be considered that there is a general deprivation of the body in bases. It is, of course, possible that there may be a localized increase of hydrogen ions in certain tissues of the body, but in the circulating blood these would always meet with hydroxyl ions for their neutralization. Magnus-Levy[6] has emphasized especially that in diabetic acidosis there is an increased accumulation rather than an increased formation of acids. A clearer statement of this position would be that there is not even any increased accumulation of acids, but that in acidosis the acids are destroyed largely by neutralization, whereas in health they are destroyed largely by oxidation.

From these considerations it is seen that the underlying principle of acidosis is a general impoverishment of the body in bases. This may be brought about by a variety of methods such as:

1. Simple starvation; *i. e.*, the withholding of bases from the food.
2. Disturbances of acid formation and elimination.
3. Loss of alkali as such during excessive purgation.

The acidoses have been classified into two groups; namely, the absolute acidoses in which there is an increase in acid, and the relative types in which there is a loss of alkali as such from the body. However, in both cases the end result is the same; that is, there is an impoverishment in bases and not an increase in acid in either case. Consequently, it would seem that there is no real distinction between the so-called relative and absolute acidoses, and that the two conditions are essentially the same. If it is necessary to subdivide the acidoses, they could be classified according to their etiology, or the effects which they produce, but it is not desirable to subdivide the principles upon which the theory of acidosis rests.

Evidence of Acidosis in Nephropathies.

The study of acidosis and the evidence for its occurrence in the nephropathies, will be considered upon the basis which has just been outlined. Among the newer arguments which have been brought forward the most important is the analysis of the alveolar air. Straub and Schlayer[7] found a definite lowering of the carbon dioxide content of the alveolar air in advanced stages of nephritis. This factor is, of course, dependent upon the carbon dioxide of the blood. It has been studied rather less than the other signs of acidosis and the authors do not draw any final conclusions from their data. Recently, a publication appeared by Lewis, Ryffel, Wolf, Cotton and Barcroft[8] upon the relation of the carbon dioxide content of the alveolar air to acidosis in cases of cardiac and renal dyspnœa. Their data upon this point are much less convincing than those of Straub and Schlayer. Lewis and his associates describe a test based upon the principle that the percentage of oxygen taken up by the blood under certain standard conditions is controlled in part by the non-volatile acids in the blood. Suggestive results were obtained in certain special cases of dyspnœa. In the data, which they report, upon lactic acid in the blood no distinction is made between lactic acid and the lactates.

Porges and Leimdörfer[9] have also found that the tension of carbon dioxide in the alveolar air is in general parallel to the symptoms of uræmia. However, a lowering of the carbon dioxide tension in the alveolar air cannot be regarded as pathognomonic of acidosis. Porges, Leimdörfer and Markovici[10] report a marked lowering in decompensated cardiac cases.

Henderson and Palmer,[11] from a study of the acidity of the urine, came to the conclusion that acidosis is an important symptom in cardiorenal cases. The method used by them consisted in the measurement of the concentration of hydrogen ions in the urine by a series of indicators. The average acidity in a group of cardiorenal cases was higher than the average acidity in a group of normals. The average of a group of nephritic cases was intermediate between the cardiorenal cases and the normal individuals. It is important to note, however, that the extreme values found in cardiorenal cases practically coincided with the extremes found in normal individuals. Expressed as negative logarithms, the extreme normal values vary from 4.82 to 7.45, with an average of 6, whereas the cardiorenal cases range from 4.52 to 7.48, with an average of 5.33.

In considering the signs by which one ordinarily recognizes acidosis in diabetes, it is evident that a true acidosis may exist in nephropathies without conforming to all of the details which are seen in diabetes. With the study of acidosis in various conditions it might be possible to determine the characteristics which are essential in any acidosis and those which are found only under special conditions. In any advanced acidosis one would expect, *a priori*, to find the following features:

I. Examination of Clinical Symptoms:
   1. Partial or complete coma.
   2. Air hunger.
   3. Bright color of the mucous membranes and the venous blood.

II. Diminution of the Carbon Dioxide of the Alveolar Air.

III. Examination of the Blood:
   1. Diminution of the carbon dioxide.
   2. Diminution of the titratable alkalinity.
   3. Relatively constant behavior of the physico-chemical reaction.

IV. Examination of the Urine:
   1. Increase in excretion of ammonium salts.*
   2. Increase in acidity.

V. Deficit of the Body in Bases (conveniently determined by the increase in tolerance to bicarbonate).

Of this list many features might be absent in mild, or even moderately severe acidoses, and would appear only under extreme conditions. The clinical signs, though very suggestive

* Except in those cases where alkali is lost from the bowel.

are not pathognomonic. The data for the analysis of the alveolar air and the titratable alkalinity of the blood are distinctly suggestive. Almost no data are available upon the carbon dioxide content of the blood. The excretion of ammonia in the urine is normal and there is no striking change in the urinary acidity. In certain types of nephropathy, especially in uræmia, a very striking increase occurs in the tolerance to bases.[12-15] Two interpretations suggest themselves very readily: namely, (1) an acidosis, and (2) retention of bicarbonate by reason of renal lesions. The explanation of this phenomenon might give conclusive evidence in regard to the presence or absence of acidosis in renal disease. The following points are suggestive of its presence:

1. The clinical signs of acidosis usually develop in typical uræmic stages.
2. Examination of the blood often shows a diminution in titratable alkalinity.
3. The kidney continues to excrete an acid urine even after massive injections of bicarbonate.

The secretion of an acid urine from the neutral or slightly alkaline blood presumably represents a definite functional activity on the part of the kidney, and not a merely passive phenomenon. If one assumes that massive amounts of bicarbonate are accumulating in the blood stream on account of the inability of the diseased kidney to excrete it, then it would be logical to expect that the kidney would cease to excrete acid. Indeed, if an excess of bicarbonate accumulated in the blood stream, then it would be difficult to explain the source from which material could be obtained for the formation of acid. Moreover, in certain cases excretion of bicarbonate may take place readily in the presence of extensive diffuse lesions of the kidney.

On the other hand, there are certain features which are not readily explained on the basis of an acidosis, such as:

1. The normal ammonia content of the urine.
2. The absence of any evidence pointing toward the presence of an excessively abnormal quantity of acids or salts of acids in the urine.

The normal excretion of ammonia points definitely against the existence of an ordinary acidosis. In accordance with this, we find that there is no excretion of any significance of the salts of organic acids, such as would correspond to the excretion of the salts of acetoacetic and β-oxybutyric acid in diabetes. It is questionable, perhaps, whether one is justified in diagnosing an acidosis on the basis of a deficit of the body in available alkalies in the absence of such cardinal signs as an increase in ammonia and in the absence of any disturbance of metabolism with a resulting accumulation of the salts of acids. It seemed desirable to obtain supplementary data in regard to these discrepancies and in regard to the fate of the bicarbonate after injection into the body. The following examinations were carried out:

I. Examination of urine:
   1. Acidity by Folin's method.
   2. Ammonia coefficient.

II. Comparison of the excretion by the kidney of:
   1. Sodium bicarbonate.
   2. Lactose.
   3. Phenolsulphonephthalein.

III. Examination of blood:
   1. Carbon dioxide content.
   2. Rest nitrogen of serum.
   3. Titratable alkalinity of serum to Töpfer's reagent and to phenolphthalein.

IV. Examination of the fæces for fixed bases after intravenous injection of bicarbonate.

A partial report of the group of cases upon which these tests were made has already been reported in connection with investigations upon titratable alkalinity. The data for the examination of the urine, the titratable alkalinity of the blood and the tolerance to sodium bicarbonate are taken from Table IV of this former publication.[14] In the present paper the tolerance to sodium bicarbonate is tabulated as deficit in sodium bicarbonate with the understanding that this is the primary factor in the explanation of these cases, though probably it is not the sole factor.

In the determinations of the tolerance to lactose, an initial injection, intravenously, of 2.5 grams was given in cases of ordinary severity. If no excretion took place, this amount was repeated in 6 or 8 hours. In the uræmic and preuræmic cases an initial injection of 5 grams, and occasionally 10 grams, was employed. The lactose was prepared by one heating for 20 minutes at 100° C. in an Arnold steam sterilizer rather than by Pasteurization, as in the routine of Schlayer. Nylander's reagent was used for its detection; the quantity excreted was not determined since it was not used as a functional test, but merely to determine whether its suppression was complete or partial. In the diuresis following the large intravenous injections of bicarbonate, it frequently happened that the urine gave no test for lactose until it had been concentrated to about one-fourth its original volume. When its presence was determined in this way a control was always carried out by concentrating a specimen of urine of the same individual obtained immediately before the injection.

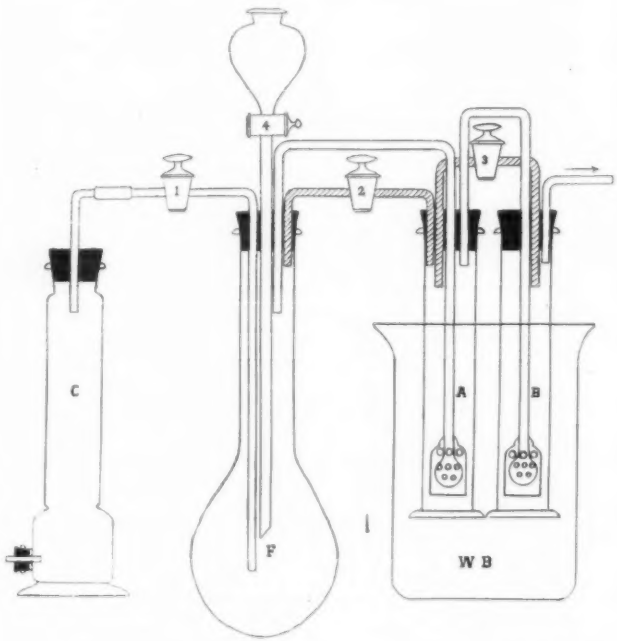
The data for phenolsulphonephthalein and rest nitrogen were very kindly supplied by Dr. Walter A. Baetjer from his investigations upon nephritis. The rest nitrogen represents the nitrogen measurable by the Kjeldahl process in the alcoholic filtrate from a 1 to 10 mixture of serum in alcohol, the serum being made very faintly acid to litmus. The mixture, after standing for a few minutes, was filtered and the filtrate gave no reaction with the biuret test for proteins.

In the uræmic cases which received large intravenous injections, the fæces and, in the cases which came to autopsy, the contents of the intestinal tract, were examined for fixed bases on account of the possibility that with defective kidney function, considerable excretion might be taking place through the intestinal tract. It frequently happened that the specimens were distinctly acid. Some of the specimens contained large quantities of ammonia. These were diluted with water and con-

centrated over the free flame until no more ammonia was given off. The data recorded in the table, therefore, represents the reaction after the removal of ammonia.

The carbon dioxide determinations of the blood are necessary on account of its importance as a sign of acidosis. Inasmuch as an advanced acidosis is required to produce significant changes in the carbon dioxide content, this determination was omitted on many of the less severe cases. Preliminary determinations were made with the Haldane-Barcroft apparatus, designed for the analysis of 1 cc. to 2 cc. quantities of blood. Inasmuch as moderate quantities of blood were available in the ordinary uræmic cases, there was no special advantage in using only minimal amounts. The determinations were carried out by an application of the method of Warburg [13] for minute amounts of carbon dioxide in water. The principle of this method is that carbon dioxide precipitates barium from a solution of barium hydrate as the carbonate. Using a known amount of barium hydrate, the excess may be determined by titration with dilute standard acid in the presence of the precipitated barium carbonate.

Certain modifications of the technique used for water were desirable in working with blood on account of the smaller volumes of material which are available and the higher content of the blood in carbon dioxide. In the first place, certain precautions were necessary for the protection of the blood specimens during their transference from the wards to the laboratory. In order to avoid loss of carbon dioxide, the blood was collected under barium hydrate and the precipitated barium carbonate was subsequently decomposed with acid. Barium hydrate was chosen because of the difficulty of securing carbonate-free specimens of the metals whose hydrates and carbonates are soluble. Throughout the work the standard barium hydrate was protected from the carbon dioxide of the air by a layer of toluene, both in the stock supplies and in the apparatus, during the absorption of carbon dioxide given off from the blood. A layer of toluene (about 1 cm.) was poured into each of the duplicate absorption cylinders. The barium hydroxide was transferred with an ordinary pipette by an open window without any appreciable error from the absorption of atmospheric carbon dioxide during the transference. After the introduction of the barium hydrate under toluene in the absorption cylinders, the entire apparatus was connected up and washed with carbon dioxide free air. For this purpose the apparatus is arranged with a double set of connections, one of which leads through the barium hydrate, the other through the air over it. This makes it possible to wash the apparatus free from carbon dioxide and subsequently, after the evolution of the carbon dioxide from the blood, to wash the gases remaining in the flask into the barium hydrate with carbon dioxide free air. The exact details were as follows: for the collection and measurement of the blood specimens, the neck of a 50 cc. graduated flask was cut off about 2 to 3 cm. above the graduation mark; 30 cc. of ½% barium hydrate solution was measured into this flask and then tightly stoppered. When the materials are handled rapidly, away from the neighborhood of flames, the error during this procedure is negligible and it is not necessary to use a protecting layer of toluene. A little more than 20 cc. of blood was taken from a vein in the arm, in the usual way, and discharged into the flask of barium hydrate up to the graduation mark, and with the needle of the syringe dipping under the surface of the barium hydrate. The flask was then stoppered and the mixture thoroughly shaken. The flasks of barium hydrate were kept in the refrigerator before use in order to minimize the error of measuring the blood at a higher temperature than that for which the flask is calibrated. Under these conditions the blood does not clot and, if necessary, the specimen can be kept over long periods before analyzing. It is preferable, however, not to allow it to stand over night, since the precipitated barium carbonate settles out over the bottom of the flask and increases the difficulty of transferring it subsequently.



Twenty cubic centimeters of N/10 barium hydrate were placed in cylinder *A* and 10 cc. in cylinder *B*. Each of these was diluted with freshly boiled water to about 75 cc. The water bath was kept at 75° to 80° C. to promote the absorption of carbon dioxide. With the double washing afforded by the Folin absorption tube and with careful heating at the beginning of the evolution of carbon dioxide, complete absorption could be obtained without the use of a third cylinder of barium hydrate. The accompanying diagram illustrates the apparatus at the beginning of the determination. *C* is a tower, 35 cm. in height, of sodium hydrate sticks; *F* is an 800 cc. short-necked Kjeldahl flask for the reaction mixture of blood and acid. *A* and *B* are the cylinders (22 x 4 cm.) for standard barium hydrate, and *WB* a hot water bath at 75° to 80° C. With barium hydrate in the cylinders *A* and *B* and with the stopcocks in the position shown in the diagram (No 4 closed and 1, 2, and 3 open) suction is applied gently and the apparatus washed for about 30

to 45 minutes to free it from carbon dioxide. Then the suction is stopped and all of the stopcocks are closed. The specimen to be analyzed is washed through the separatory funnel with about 200 cc. of freshly boiled water and followed by about 12 to 15 cc. of 20% orthophosphoric acid. The reaction mixture is then heated for 10 or 15 minutes at the boiling point. This can ordinarily be done without the use of paraffin to prevent foaming. The use of paraffin makes the evolution of steam less regular and increases the tendency of the fluid in the absorption cylinders to suck back. The long absorption tubes projecting above the cylinders were used to lessen the danger from this source. When the heating is finished, the stopcock No. 1 is again opened and a current of air is carried through the apparatus for about 30 minutes. The excess of barium hydrate is then titrated in the absorption cylinders with N/28 hydrochloric acid against phenolphthalein.

The calculation of the results under these conditions is very simple. The burette reading in cubic centimeters subtracted from 84 and multiplied by 2 gives the volumes per cent of carbon dioxide. Eighty-four is the equivalent in N/28 solution of 30 cc. of an N/10 solution. The cubic centimeters of N/28 solution neutralized by the carbon dioxide, when multiplied by 0.4, gives the cubic centimeters of carbon dioxide at 0° C. and 760 mm. in 20 cc. of blood. (One cubic centimeter of an N/28 solution for reaction with barium hydrate is equivalent to 0.4 cc. of carbon dioxide under standard conditions.) This product multiplied by 5 gives the cubic centimeters of carbon dioxide in 100 cc. of blood, or the volumes per cent of carbon dioxide.

The accuracy of this method was tested upon 20 cc. quantities of a solution of sodium carbonate containing 45 volumes per cent of carbon dioxide (N/25), and upon normal human blood. The analyses of the carbonate solutions were accurate in actual practice to within 3 to 5 volumes per cent though test cases could be run a little closer. The relative error is comparatively large though the absolute error is small. The following analysis illustrates this:

	Calculated	Found	Error in volumes %
Grams CO_2	0.0176	0.0164	
Volumes %	45	42	3

The analysis of six specimens of normal venous blood gave values ranging from 44 to 52 volumes per cent.

A brief synopsis of the clinical data is given in the table in order to provide a general impression of the type of cases on which these tests were made. Of the patients who showed heart lesions, all were tested at a time when the compensation was good. Those who were subject to frequent breaks were tested after an interval of not less than two or three weeks after the last break. All of these cases were given a normal mixed diet at the period when these tests were made with the exception of the uræmic patients. In the stage of uræmia, the intake of carbohydrates was usually limited but it was not reduced sufficiently to give rise to acetonuria in any instance. The tests for acetone with sodium nitroprusside were negative in all of the cases in the table on pages 148 and 149.

ANALYSIS OF TABLE I.

Comparison of the Behavior of Bicarbonate with Substances which are Suppressed by Renal Lesions.—This table illustrates several important features. In the first place, the excretion of bicarbonate is essentially different from those substances which are suppressed during renal insufficiency. In addition to the substances recorded in the table, all of these patients were excreting a certain amount of chlorides even upon a diet in which the chlorides were restricted. However, the chlorides, lactose, phenolsulphonephthalein and the water, were not completely suppressed, even when the intake of these substances was comparatively small in amount. Thus not more than 10 grams of lactose, nor more than 0.0012 gram of phenolsulphonephthalein were required in the most severe cases to produce some excretion in the urine. On the other hand, the bicarbonates were often completely suppressed even in quantities as high as 160 grams. This establishes a rather sharp difference between the bicarbonate and a fairly representative group of substances which are known to be suppressed by renal lesions; namely fluids, salts, sugars and dyes.

Carbon Dioxide Content of the Blood.—The content of the venous blood in carbon dioxide is sufficiently low to be practically pathognomonic of acidosis. In four typical cases the values varied from 10 to 24 volumes per cent as compared with a normal of 44 to 52 volumes per cent. Under the conditions which occur in uræmia it is difficult to explain this reduction by other factors.

Ammonia Excretion.—The ammonia excretion in the cases uncomplicated by hepatic lesions is distinctly normal. This at once raises the question as to whether there is no increase in the accumulation of ammonia, or whether it accumulates in the blood by reason of renal insufficiency. Comparatively large amounts of ammonia were found in the intestinal tract in the examination of the fæces for fixed bases. This might appear to lend superficial support to the view that this ammonia is excreted by way of the intestinal tract by reason of renal insufficiency. On account of the accumulation of urea in the body and its excretion into the intestine, this ammonia can be accounted for much more logically by the fermentation of urea. Furthermore, the values for the rest nitrogen of the blood practically excluded the accumulation of any significant quantity of ammonia in the blood, which would in any way be comparable to the excretion of ammonia in even moderate grades of diabetic acidosis. Thus, in three cases (H, K, and M) the values for rest nitrogen fall within normal limits although the tolerance to bicarbonate is definitely increased. Moreover, in those cases where the rest nitrogen is high this increase can be accounted for largely by the increase in the urea fraction. The investigations of the French school have shown that urea is quantitatively the most important constituent of the rest nitrogen, both in the normal and in nephritic individuals. Weill has recently reviewed this subject.[16]

Reaction of Fæces.—The reaction of the fæces is important. It demonstrates that the injections of bicarbonate were retained within the body. In some cases the intestinal contents were

acid. In Case A, who received in all 160 grams of bicarbonate, an alkaline reaction of the faces was not obtained after any of the injections or at section. In another patient, D, in whom 70 grams of bicarbonate were injected, the intestinal contents at section were found to be slightly acid to litmus. No free ammonia was present in these specimens.

Effect on Clinical Symptoms.—Observations on the effect of the administration of bicarbonate were made with especial reference to three features, namely: coma, dyspnœa, and the total output of urine. Of the seven cases in uræmia, five were sufficiently comatose to be either practically or wholly unable to respond to simple questions. In one of these, B, there was no change in his mental condition. Of the other four, one came out completely from the uræmia, though this result was probably not to be attributed to the bicarbonate. In the other three there was distinct improvement in the mental condition, which could be directly attributed to the injections, though none of these recovered completely from their stupor. The improvement was shown by a diminution in their restlessness and by their ability to answer questions, and even to carry on a limited conversation. In one patient, C, the improvement appeared within a few hours after the administration of 30 grams of bicarbonate, whereas in another, A, no change was noted till 100 grams had been injected. The air hunger which existed in three cases (A, C and D) was definitely relieved by the injections. The respiratory changes in two patients (H and J) were especially interesting. These men had continual dyspnœa which did not disappear even upon rest in bed. However, after the administration of bicarbonate, this dyspnœa disappeared completely and did not return during the several weeks that they remained in the hospital. In a third case (L) the dyspnœa was not affected by an amount of bicarbonate sufficient to render the urine alkaline.

The effect upon the excretion of urine was not especially noticeable in the cases with a normal output. In the cases with oliguria the output improved as a rule, though exact measurements were often very difficult on account of the incontinence of many of these patients. In two instances (A and D) a definite polyuria followed the injections, and in a third case, with anuria of 15 hours duration, a polyuria developed within 8 hours after the injection.

Summary of the Data in Table I.

In summarizing this evidence, then, we have a striking increase in the tolerance to fixed bases in many nephritics. The parallelism between this increase in tolerance and the impoverishment of the blood in titratable alkali is crucial evidence of a marked deficit of the body in bases or in substances which readily give rise to bases. This deficit is often sufficient to give rise to definite clinical symptoms. In four cases of uræmia, the carbon dioxide content of the blood was markedly lowered. These features justify the diagnosis of an acidosis of high grade on the basis that the essential feature of acidosis is an impoverishment of the body in bases or in substances which readily give rise to bases. Such an acidosis is characterized by:

1. An increase in the tolerance to bases.
2. Decrease in the titratable alkalinity.
3. Decrease in the carbon dioxide content of the blood.
4. Normal excretion of ammonia.
5. Absence of any disturbance of carbohydrate or fat metabolism.

The question was raised as to whether the bicarbonate injected in the uræmic cases is retained as such, or whether it is retained on account of an acidosis. It is seen that this question requires a little modification. In any case, even in an acidosis the bicarbonate which is injected is retained as such, that is for use as an alkali. The point at issue, is whether the bicarbonate is retained in considerable excess over the normal content of the blood on account of the failure of the kidney to excrete it, or whether it is retained to replace a deficit of carbonates in the blood and other tissues. The latter explanation is clearly the correct one. It seems probable that after the urine has been rendered alkaline by bicarbonate, an insignificant amount might be retained on account of renal suppression; but practically all of the bicarbonate is retained to restore the content of the tissues to normal.

Definition of Acidosis.

A priori, it is to be considered that an increase in the excretion of ammonia is an essential feature of acidosis. However, there are cases of nephritis and uncomplicated diabetes which show a definite change in the titratable alkalinity and a significant increase in their tolerance to bicarbonate without an increase in ammonia. Such cases justify the conclusion that an acidosis is not necessarily accompanied by an increase in the excretion of ammonia. The changes from the normal metabolism to a state of acidosis are purely quantitative. It is evident that there is no natural division, and any such division in the early stages would necessarily be purely artificial. By definition, then, an acidosis is a general impoverishment of the body, from any cause, in fixed bases or in substances which readily give rise to fixed bases. The essential fundamental features that have been established thus far which would be common to all acidoses are:

1. An increase in the tolerance of the body to fixed bases.
2. A diminution of the titratable alkalinity of the blood serum.
3. A diminution of the carbon dioxide of the blood.

These are the features which are well understood and are readily susceptible of demonstration. They would, of course, be accompanied by related changes; a low carbon dioxide content of the blood should result in a low tension of carbon dioxide in the alveolar air, an analysis which is not always satisfactory in a comatose patient, or in one who is, for any reason, unable to co-operate. Similarly, the reduction of the titratable alkalinity might be accompanied by a slight increase in the excretion of neutral salts in the urine, but it is evident that it might readily be well-nigh impossible to detect this change in excretion. The ammonia content of the urine is by no means an absolute criterion of the presence or absence of acidosis. It may be normal even in moderate grades of dia-

betic acidosis. On the other hand, the relative and absolute amounts of ammonia may be comparatively high in certain toxæmias in which acidosis is absent; a toxæmia of pregnancy was reported in which the daily output of ammonia was as high as two grams and the coefficient reached 40% under conditions in which acidosis could be excluded.[12] There is one condition which definitely would not come under this definition of acidosis; namely, the localized accumulation of acid in special organs or tissues, such as Fischer[17] has described as occurring in the kidney.

Two methods are available for the detection of these features of acidosis; namely, the reaction of blood serum to phenolphthalein and the effect of the ingestion of sodium bicarbonate upon the reaction of the urine. These methods have given evidence of acidosis of varying grades in diabetes, in nephropathies, in anæmias, and in rheumatic fever. Either of them would presumably be applicable in the detection of acidosis from any cause whatever. The details of these tests are very simple. For the first, 1 cc. of serum is added to 25 cc. absolute alcohol and the mixture shaken thoroughly. The precipitated proteins are filtered off and the alcoholic filtrate, without washing the precipitate, is evaporated to dryness with a few drops of phenolphthalein solution, taking care to avoid dilution of the alcohol from an excess of steam during evaporation. In the earliest changes from the normal the alcoholic filtrate becomes red, but the residue after evaporation rapidly loses its color at the temperature of the water bath (5 to 15 minutes), whereas the normal specimens retain their color for several hours. Details of the more advanced changes are given in reference No. 14.

The test by means of sodium bicarbonate is equally simple. Five grams of sodium bicarbonate are given by mouth unless gastrointestinal complications that would interfere with absorption are present. In that case intravenous injection may be used. Preferably, the patient should void at the time of administration of the bicarbonate. Practically any normal individual, on an ordinary mixed diet, will react, usually in about 3 hours, by excreting a urine which is neutral or alkaline to litmus. When a specimen does not react sharply to litmus paper, a few cubic centimeters should be thoroughly boiled in a test tube to promote the change of bicarbonate to normal carbonate. Specimens which are faintly acid to litmus before boiling may react slightly alkaline to litmus after boiling. In cases which do not react the bicarbonate may be repeated in increasing quantities such as 20 or 30 grams at intervals of 3 to 6 or 8 hours, the reaction of the urine being tested before each repetition. In some cases massive quantities may be given without affecting the reaction of the urine, *e. g.*, 150 grams in 1 to 2 days.

It is possible in a general way to determine the physiologic effect of various grades of depletion in bicarbonate. A deficit of as much as 20 grams can be detected by the examination of the blood, but certainly does not give rise to any symptoms. A deficit of approximately 40 grams causes a sharper change in the behavior of the blood, but still does not give rise to any appreciable dyspnœa even on exertion. With an increase in this deficit to 70 or 80 grams, three patients showed dyspnœa which persisted in two of them, even when at rest in bed. It is difficult to determine even the approximate quantities which would cause the more advanced symptoms of stupor and coma, since other factors often contribute to the production of these symptoms. In two cases which were observed a condition of air hunger and partial coma was relieved temporarily by the injection of 130 and 160 grams respectively. It seemed clear that this deficit would have been the immediate cause of death in these cases and one may assume that such quantities approach the limits which would be fatal in the depletion of the body in fixed bases. These figures are slightly lower than the highest values obtained in diabetic coma in which a deficit of 200 grams has been reported.[18] The interpretation of the figures in diabetes is complicated by the rapid formation of acid and the compensatory neutralization by ammonia. In fatal cases it seems probable that the unexhausted supply of fixed bases is only a minimal quantity; therefore, it would not be surprising to find that the total available supply of substances in the body yielding fixed bases is in the neighborhood of the equivalent of 200 grams of sodium bicarbonate, or at least of that general order of magnitude.

Clinical Significance.

There are several factors bearing upon the significance of the acidosis observed in these cases. In the uræmic cases, the severity of the condition of the individual patients was by no means proportional to the degree of acidosis. In some patients the lack of carbonates was extreme, while in others the deficit was so slight that no symptoms of dyspnœa developed. In one case (L) the dyspnœa was not typically cardiac and was apparently of renal origin yet it was definitely not due to acidosis. From these considerations, it seems evident that acidosis is only a secondary factor and that it is the result, and not the cause, of the renal lesions. However, it does not develop merely as a terminal event, but is present in an appreciable degree in ordinary grades of nephritis. The evidence at hand shows that there may be definite signs of chronic interstitial lesions, accompanied by moderate subjective symptoms without any appreciable grade of acidosis. On the other hand, it is equally definite that an acidosis sufficiently severe to produce symptoms of dyspnœa may develop at least many months before any signs of uræmia appear. Furthermore, this acidosis may be so extensive as to play an important rôle in the symptomatology of uræmia and even to constitute the immediate cause of death. That it is seldom, if ever, the sole cause of death is strongly indicated by the merely transient benefit following the injection of bicarbonate in the uræmia of chronic cases. Some of the symptoms resembling toxæmia in uræmia are due, not altogether to the presence of a foreign toxin, but in part to the depletion of the body in one of its normal constituents. Therefore, the therapeutic bleeding for the removal of any toxins that may be circulating in the blood causes at the same time a still further diminution of a substance which is already seriously depleted. This disadvantage could be

TABLE I. EXAMINATION OF CHRONIC D

CASES [illegible]URÆMIA

CLINICAL RECORD.							Urine.						
Case.	Age.	Respiration with regard to dyspnœa.	Heart.	Sclerosis of arteries.	Average blood pressure (mm. of Hg.).	Œdema.	Fluid balance (average daily output).	Acidity in % of N/1 solution.	Ammonia coefficient.	Deficit in sodium bicarbonate (grams).	Reaction of urine to litmus after bicarbonate.	Tolerance to lactose (grams.)
A	48	Air hunger	Hypertrophied, compensating.	Well marked	190	Polyserositis	500 cc	3.5%	3.0%	160+	Acid	10
B	29	Well-marked dyspnœa.	Normal	Moderate	140	Well marked	Normal	2.3%	3.5%	40+	Acid	5
C	60	Air hunger	Well marked hypertrophy, compensating.	Well marked	180	None	Anuria 15 hrs.			30+	Acid	10
D	57	Air hunger	Hypertrophied, compensating.	Well marked	220	None	Com'ncing oliguria.	1.5%	2.4%	70	Neutral	5
E	64	No air hunger. Moderate dyspnœa.	Hypertrophy. Frequent breaks	Well marked	240	Well marked	Normal	3.8%	5.2%	30	Amphot[illegible]	10
F	40	None	Hypertrophied, compensating.	Moderate	210	None	Polyuria	2.7%	4.0%	30	Neutral	5
G	40	No dyspnœa	Normal	Well marked	180	Slight	Oliguria	2.5%	3.5%	40	Alkaline	
EXTREME CASES WITH ADV[illegible]CED SU[illegible]												
H	55	Frequent attacks of dyspnœa.	Hypertrophied, dilated. Frequent breaks.	Moderate	170	Moderate	Oliguria 500 cc.	3.0%	3.7%	70 [2]	Alkaline	2½
I	40	Dyspnœa on exertion.	Hypertrophied, compensated.		190	Slight	Normal	3.1%	4.2%	80 [2]	Alkaline	2½
J	44	Constant dyspnœa.	Hypertrophied, dilated. Frequent breaks.	Well marked	200	In lower extremities.	Polyuria	2.5%	2.6%	70 [2]	Alkaline	5
K	35	None	Partially compensated on admission.		140	Well marked	Polyuria	2.0%	8.7%	80	Alkaline	2½
L	52	Constant. Well marked.	Dilated. Partially compensated on admission	Slight	160	Moderate	Normal	2.0%	11.6%	40	Alkaline	
OUTSPOKEN CASES WITH MORE OR [illegible]SS DEFI[illegible]												
M	41	Cheyne-Stokes, with marked dyspnœa.	Frequent breaks	Well marked	170	Well marked	Polyuria	4.0%	7.1%	30 [2]	Alkaline	2½
N	49	Slight dyspnœa	Acute mitral endocarditis.	Moderate	140	Moderate	Normal	1.5%	11.8%	30 [2]	Alkaline	2½
O	67	Normal	Hypertrophy, compensated.	Slight	160	Puffiness, face.	Normal	2.7%	3.0%	20 [2]	Alkaline	2½
P	54	Normal	Slight hypertrophy	Moderate	190	Puff'n's, eyelids	Normal	2.4%	2.2%	10 [2]	Alkaline	2½
Q	39	Normal	Slight hypertrophy, compensating.	Moderate	200	None	Normal	1.8%	4.0%	10 [2]	Alkaline	2½
Normal average.								1% to 3%	2% to 5%	5	Alkaline	2½

[1] No color after 5 minutes. [2] By ingestion. [3] Six days

OF CHRONIC DIFFUSE NEPHROPATHIES.

ASES OF URÆMIA.

RENAL FUNCTION.											
			Blood.	Blood serum.						Reaction of fæces to litmus after removal of NH_3.	Subsequent record (or pathological diagnosis).
	Tolerance to lactose (grams.)	Excretion of phenolsulphonephthalein (% in 2 hrs.).	% of CO_2.	Rest nitrogen grams per liter.	Alkalinity to Töpfer's in % N/1 solution.	Behavior toward phenolphthalein.					
						After removal of protein.			1 to 10 dilution of whole serum in water.		
						In alcoholic solution.	Residue after evaporation.	In aqueous solution.			
id....	10	18%[2]	20%	2.1	0.6%	No color...	No color...	No color...	No color...	Neutral or acid	Death two days later. Chronic diffuse nephritis.
id....	5	Trace...	10%	2.0	0.9%	No color...	No color...	Pink.....	Red	Neutral.....	Death one day later. Acute exacerbation of chronic diffuse nephritis.
id....	10	Trace...	24%	.....	0.6%	No color...	No color...	No color...	Pink.....	Slightly acid...	Slight cardiac hypertrophy. Death one day later. Chronic diffuse nephritis.
utral	5	Trace[1]...	22%	.....	0.8%	No color...	No color...	No color...	No color...	Slightly acid...	Death three days later. Chronic diffuse nephritis.
phot	10	35%	.....	0.5	0.8%	Pink.....	(3)	Red	Red	Neutral.....	Recovery from uræmia. Death six weeks later with broken compensation and early bronchopneumonia. Chronic diffuse nephritis.
utral	5	Trace...	.....	0.6	0.7%	No color...	No color...	Pink.....	Pink.....	.....	Left hospital in serious condition.
aline	.....	Trace[1]...	.....	.....	0.8%	Pink.....	(3)	Red	Red	.....	Death three days later.
ADVANCED SUBJECTIVE SYMPTOMS.											
aline	2½	35%	39%	0.3	0.6%	No color...	No color...	Pink.....	Red.....	Slightly alkaline.	Death eleven months later. No section.
aline	2½	35%	35%	0.7	0.8%	No color...	No color...	No color...	Red.....	Slightly alkaline.	Left hospital after six weeks without subjective symptoms when at rest.
aline	5	Trace...	35%	1.0	1.0%	No color...	No color...	No color...	Faint pink.	Slightly alkaline.	Death eight months later. No section.
aline	2½	50%	.....	0.2	0.8%	No color...	No color...	Red.....	Red.....	Slightly alkaline.	Death three months later. Early luetic hepatitis. Chronic diffuse nephritis. Positive Wassermann.
aline	.....	.....	.....	.....	0.7%	No color...	No color...	Red.....	Red.....	.....	
OR LESS DEFINITE SUBJECTIVE SYMPTOMS.											
line	2½	25%	42%	0.2	0.9%	Red.....	(3)	Red.....	Red.....	.....	
line	2½	20%	51%	.....	1.0%	Red.....	(3)	Red.....	Red.....	.....	Diffuse cirrhosis liver.
line	2½	25%	42%	.....	1.0%	Red.....	(3)	Red.....	Red.....	.....	
line	2½	35%	.....	.....	0.8%	Red.....	Red.....	Red.....	Red.....	.....	
line	2½	.....	.....	.....	1.3%	Red.....	Red.....	Red.....	Red.....	.....	
ine	2½	65%	45% to 50%.	0.3	1.0%	Red.....	Red.....	Red.....	Red.....	.....	

[2] Six days before death. [1] After 0.0012 gram.

readily obviated by the injection of bicarbonate though special precautions might be necessary in the many cases where the bleeding is done primarily for the relief of some mechanical embarrassment to the circulation.

Diagnosis of Uræmia.—The wide variation in the degree of acidosis in these cases of uræmia raises the question as to whether cases may not occur in which it is absent altogether. No such instances have been encountered; the readiness with which slight grades of acidosis can be detected, and the frequent appearance of the milder grades, even in cases of only ordinary severity, would indicate that chronic uræmias without any acidosis would be at least comparatively rare. In the diagnosis of uræmia there is often an opportunity for considerable variation of opinion. The similarity of the symptoms which may result from cardiac, renal, and cerebral lesions sometimes renders differentiation rather difficult; in complicated cases where changes in all of these organs are present, it may be impossible to determine what features predominate. It seems probable that metabolic changes occur in these cases which can be correlated with the clinical features. The examination of the blood and urine for such factors as the titratable alkalinity, rest nitrogen, and the renal function in conjunction with the clinical picture might enable one to differentiate more sharply certain types of these cases. The cases of uræmia reported in this paper were by no means free from cardiac and cerebral complications, but only those types were selected in which the uræmic symptoms predominated very definitely.

Clinical Estimation of the Degree of Acidosis.—Several methods have been proposed for the rapid clinical estimation of the degree of acidosis in diabetes. A review of this subject by Addis [19] appeared recently. They depend, for the most part, upon the simplified methods for estimating β-oxybutyric and acetoacetic acid or acetone. Obviously, such methods are particularly applicable to diabetes. In renal disease, as a preliminary step, the examination of the titratable alkalinity is desirable, since it gives information at once at to whether the administration of bicarbonate is urgent and also an idea of the amount which will be required. The determination of the tolerance to bicarbonate combines in one step a measure for therapy and a method for comparing the extent of acidosis in different individuals.

Relation of the Acidosis to Salt Action and to Therapy.—In considering the treatment of the acidosis of nephropathies one may ask how much good may be expected and also what dangers there may be from the use of the comparatively large amounts of salt that are often necessary, on the basis that the effect of salt in the production of œdema is due to the general properties of salt action. In regard to this latter point it is important to remember that one is not increasing the carbonates above the normal, but merely replacing a deficit of this salt. It is important to know the effect of bicarbonate upon the excretion of urine, the production of œdema, and the work of the heart. As regards the excretion of urine, there is a definite tendency of the bicarbonate to cause an increase in the total output. It might be expected that in the advanced uræmias the injection of massive doses of bicarbonate during a period of one to two days would tend to produce an œdema. However, the fluid balance was not disturbed, or else a polyuria resulted. In cases where there was a pre-existing œdema, there was no tendency for it to increase or diminish. When acidosis develops in the uræmia of chronic renal disease its treatment by massive injections of bicarbonate offers not more than relief from air hunger and temporary improvement in the mental condition and general comfort of the patient. The effect on uræmia of the early treatment of acute nephritis can best be studied in Asiatic cholera. In this disease acute nephritis occurs in all severe cases and uræmia develops with surprising regularity. Where treatment was instituted early in the course of the disease it was found that no deaths from uræmia occurred in a series of 76 cases, whereas in a corresponding control series there were 10 deaths from uræmia.[20] On the other hand, the chronic nephritides extend over such a long period of years that it would be extremely difficult to determine the effect, in regard to the subsequent development of uræmia, of the early administration of therapy before the signs of an outspoken acidosis had appeared. The treatment of the early grades of acidosis would be a simple and rational procedure and would seem to offer some possibility of exerting a favorable influence upon such a slowly progressive condition as chronic nephritis.

It is obviously necessary to establish the existence of acidosis in each individual patient in preference to the routine treatment of all cases as recommended by v. Hösslin.[21] This is readily accomplished, either by the examination of the blood serum with phenolphthalein, or by the administration of increasing quantities of bicarbonate until an alkaline reaction of the urine is produced. The choice of carbonates for administration is important, especially for intravenous injection. The normal carbonate destroys red blood corpuscles rapidly in vitro, causing extensive hæmolysis and discoloration of hæmoglobin, even in the presence of serum. While such action probably does not take place in vivo, yet it is conceivable that less evident injury may occur. One argument which has been advanced in favor of the normal carbonate is that it can take up additional carbon dioxide, relieving the internal respiration, whereas the bicarbonate cannot take up any additional carbon dioxide. However, this would not seem to be important, since the bicarbonate, on passage through the lungs, gives off carbon dioxide and can then take up more from the tissues for transportation to the lungs. Weight for weight, sodium bicarbonate neutralizes only about five-eighths as much acid as the carbonate. Concentrations of 4 or 5%, however, cause no hæmolysis of washed red corpuscles in vitro, whereas, fractions of a per cent of the carbonate are very active against red cells producing hæmolysis and discoloration of the hæmoglobin even in the presence of serum. Accordingly, very much stronger solutions of bicarbonate can be used than would be advisable with the normal carbonate. The relatively long duration of the effect of bicarbonate [14] is a hopeful feature in therapy of nephritic conditions as contrasted with the short duration in diabetic coma.

Treatment of acute nephritis by the injection of massive

doses of carbonate and neutral salt was carried out by Hogan and others at the suggestion of Fischer.[11] These injections have been performed on the basis that an acidosis occurs in all acute nephritides without determining its existence in the individual patients. Furthermore, the quantity to be administered was determined by the clinical symptoms without reference to the reaction of the urine. More recently Fischer[12] has suggested that the reaction of the urine be followed as a guide to the quantity of carbonate to be administered. In this paper I have not considered the relief of nephritis by the employment of salt action *per se*. The conclusions which have been obtained in regard to acidosis differ from those of Fischer in two respects; namely, (1) that a localized accumulation of hydrogen ions in certain organs or tissues of the body is not considered to be an acidosis in the generally accepted sense of the term, and (2) the impoverishment in bases which reaches its maximum in uræmia represents an effect and not the cause of the renal condition.

Etiology.—In considering the etiology of this acidosis of renal disease it is evident that the carbonates are depleted not by their loss as such from the body, but through chemical action. The only logical possibility of their destruction by chemical action is through neutralization by acids. The most obscure factor is the source from which such acids could come. No evidence appears in the literature of the presence of any abnormal acids or salts of acids in the blood or urine of nephritic cases. One of the normal functions of the kidney is the production and excretion of acids from a neutral or slightly alkaline blood. With the impairment of the other functions of the kidney it seems not unlikely that this functional activity is also impaired, with the result that there is a very gradual decrease in the excretion of acid in the urine and a corresponding reduction of carbonates in the blood corresponding to the amount of acid salts which are suppressed. Such an explanation would account for the long duration of the effect of the administration of carbonates in renal disease as contrasted with diabetes. It is noteworthy that the extent of the acidosis is roughly parallel to the signs of renal suppression. In Table I the cases which show a high deficit in bicarbonate also show definite retention of rest nitrogen. In some of the parenchymatous nephritides Baetjer[13] has found evidence of increased permeability of the kidney; the parenchymatous type of case shows no evidence of acidosis. The excretion of ammonia is also interesting. In diabetes the high ammonia values of the urine result, not from an increased formation of ammonia, but from an interception and neutralization of ammonia in the tissues by acid during the process of the formation of urea. In the nephropathies, however, it is quite possible that in the blood stream there would be no ammonia available for the neutralization of the acid salts which the kidney fails to excrete. As these salts tended to accumulate in the blood neutralization by the carbonates would take place. The following is a summary of the points which lend support to the view that this deficit of the body in bicarbonate is due to an impaired activity of the kidney in its function of excreting acids:

1. The signs of acidosis are proportional to the signs of renal suppression.
2. The effect of the administration of carbonates lasts for comparatively long periods.
3. The normal excretion of ammonia could be explained by the lack of any considerable quantity of ammonia in the blood stream which could be intercepted by acids.

On this basis one would expect to find the acidity of the urine decreased rather than increased in chronic renal disease. Henderson and Palmer[14] have carried out extensive examinations of the hydrogen ion concentration of the urine and their observations do not support this view very strongly. The average acidity in a group of renal cases without cardiac decompensation was slightly higher than the normal average, but not so high as the average in a group of decompensated cardiorenal cases. Of the individual cases, three were found to be at the lower limits of normal, while the remaining 11 cases were all higher than the normal average, but only one occurred which was higher than the normal maximum.

It is noteworthy that even after very extensive destruction of the renal tissue with a marked impairment of practically all of its functions, the organ still retains its ability to excrete acids in a remarkable degree. Patients in fatal uræmia, developing in the course of a chronic or acute nephropathy, continue to excrete a urine of distinctly acid reaction. Indeed, it seems that fixed bases are excreted only when they are introduced into the body in excess. The ability of the kidney to excrete acid salts is apparently one of the last functions to be lost, persisting as long as fluid is excreted.

Conclusions.

I. The essential feature in acidosis consists in a general impoverishment of the body in bases or in substances which readily give rise to bases; *e. g.*, sodium carbonate. The impoverishment in bases may be brought about by the loss of bases as such, as in the so-called relative acidosis, or by the neutralization by acids as in the so-called absolute acidosis. In either case the end result is the same and the distinction between relative and absolute acidoses is misleading.

II. The fundamental features of every acidosis which have been established thus far are:

1. An increase in the tolerance of the body to fixed bases.
2. A diminution in the titratable alkalinity of the blood serum.
3. A diminution in the carbon dioxide of the blood.

III. The excretion of ammonia either in its relative or absolute amounts does not afford a definite basis for the detection of acidosis. Thus:

1. The ammonia excretion may be normal in acidosis. This may occur in diabetic cases which are free from any suggestion of renal disease. In the nephritic cases in which the ammonia is low in the urine it is probable that there is no increase in the quantity of ammonia in the blood though some have suggested that it accumulates in the blood and its excretion in the urine is suppressed.

2. The ammonia excretion may be increased even to the extent of 2 grams per day with an ammonia coefficient of 40%, in conditions in which there is no acidosis.

IV. An acidosis of high grade occurs in certain nephropathies. The acidosis reaches its maximum in the uræmia of acute and of chronic diffuse nephropathy. It is not a terminal event, for it is often present in relatively high grade in outspoken cases many months before the development of uræmia. It represents the effect rather than the cause of the renal lesions and thus constitutes a condition of only secondary importance.

V. The characteristics of the chemical pathology of this acidosis are:

1. Increase in tolerance to bases.
2. Decrease in titratable alkalinity of the blood.
3. Decrease in the carbon dioxide content of the blood.
4. Normal excretion of ammonia.
5. Absence of any disturbance of carbohydrate or fat metabolism, and absence of the salts of any abnormal organic acids.

VI. The changes in the titratable alkalinity of the blood which can be detected by the use of phenolphthalein afford a ready means for the prompt diagnosis of acidosis and the method is particularly applicable in renal disease. In this condition it furnishes a definite indication of the amount of bicarbonate that will be required for the relief of the acidosis. The determination of the tolerance of the body to sodium bicarbonate also affords a delicate method of general application for the detection of acidosis.

VII. Examination of the fæces showed that bicarbonate was not excreted into the intestine even in the cases in which massive doses were injected.

VIII. Some of the toxic symptoms of uræmia are due, not to the presence of a toxin, but to the absence of a normal constituent of the blood, namely, the carbonates. Therefore, the therapeutic bleeding for the removal of any toxins that may be circulating causes at the same time a still further diminution in a substance in which the blood is already seriously depleted. This disadvantage could be readily obviated by the injection of bicarbonate at the time of bleeding.

IX. This acidosis is perhaps the result of defective function of the kidney in the normal separation and excretion of acid salts. If this supposition is correct, the acidosis would be an *indirect expression* of renal retention. In support of this it has been found that the acidosis is in general parallel to the ordinary signs of renal retention, such as the suppression of the excretion of dyes and sugars and the accumulation of non-protein nitrogen in the blood.

Discussion.

This evidence of acidosis offers a satisfactory explanation for some of the clinical symptoms which occur in uræmia. The coma in some cases is due to an impoverishment of the body in bases and can be partially relieved by the injection of bicarbonate. In uncomplicated cases the typical air hunger which sometimes develops and the accompanying bright color of the mucous membranes is another expression of acidosis.

In the acute nephritis of Asiatic cholera, the early administration of massive injections of sodium bicarbonate results in permanent benefit. Chronic diffuse lesions lead eventually to the development of acidosis, which if not treated will progress to such an extent as to produce the clinical picture of air hunger. In the stage of uræmia acidosis sometimes constitutes the immediate cause of death. In the selection of carbonates for therapy, the bicarbonate meets the essential requirements. The administration of the normal sodium carbonate is regarded as unnecessary and inadvisable. In any acidosis the administration of bicarbonate may be continued until the urine becomes alkaline, even though extensive renal lesions are present.

In the nephropathies which show an increase in tolerance to sodium bicarbonate this salt fails to be excreted, not on account of defective elimination by the kidney, but because there is a deficit of carbonates in the body. When the content of the body has been restored to normal, excretion of bicarbonate takes place and the urine becomes alkaline in reaction.

One of the principal points in this paper is that an acidosis of high grade may occur in the absence of any disturbance in the carbohydrate metabolism and without producing an increase in the excretion of ammonia. Important confirmation of this would be obtained if one could establish an experimental method for the production of acidosis without increasing the output of ammonia. It would also be helpful to know the effect of general anæsthesia upon renal patients in whom the respiratory mechanism is already overtaxed by an acidosis.

If one distinguishes between a disorder of metabolism and an intoxication, then the spontaneous acidoses should be classed as a disorder of metabolism and the term "acidosis" is perhaps more appropriate than "acid intoxication."

This investigation has been conducted in the clinic of Prof. L. F. Barker; it is a pleasure to express my appreciation to him for a stimulating interest in this work.

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THE WORK OF THE OUT-PATIENT DEPARTMENT OF THE HENRY PHIPPS PSYCHIATRIC CLINIC.*

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The number of patients registered in the dispensary of the Henry Phipps Psychiatric Clinic since its opening on May 1, 1913, is 543. These patients presented symptoms of mental disorder varying in type and degree. In view of the fact that there is a rather vague idea in the profession at large as to the concrete problems dealt with in such a dispensary, a few preliminary remarks may be excused.

Mental disorder means a disorder of the biological activity of the individual which is shown in its higher adjustments; such a disorder cannot be understood without taking into consideration the complex activities of the individual, not only the chemical, the metabolic and physiological adjustments, but those still more complex adjustments which cannot be adequately described under terms that do not include the concept behavior. The more complex adjustments, however, may be interfered with by processes which act at various levels of the patient's activity; thus gross damage to the brain by injury may result in very peculiar conduct, or the adjustment to the environment may be interfered with by the acute or chronic action of poison introduced from without, such as alcohol or lead, or developed within the organism, as in pneumonia or typhoid. Or the source of the disorder may lie in alterations in the secretions of the ductless glands, or again the disorder of adjustment may be the result of such changes of the brain as are caused by arteriosclerosis or the senile alterations. Clinical experience, however, forces one to recognize many disorders of adjustment in which no primary disorder at any of these levels can be demonstrated, but where, from more complex causes, the mood of the patient is altered or the general activity changed in type or in quality, or where the patient tries to adjust himself to the environment by subtly transforming his own conception of that environment, leading to those symptoms which the observer describes as delusions and hallucinations. In the evolution of these latter disorders of conduct, the difficulties inherent in the individual present as a rule the most important problem, but the exact test presented to him by the environment and the amount of strain which this puts on the individual's power of adaptation must never be ignored, and sometimes is the important factor open to modification.

The above remarks may show how necessary it is in dealing with a case of mental disorder to keep in mind the possibility of a primary disturbance at various levels of the patient's activity. The physician must make sure that the simpler mechanisms are intact before he inculpates the more elaborate mechanisms. An adequate physical examination is, therefore, the basis of any satisfactory psychiatric examination. An examination of a mental case is thus rather complicated and can ignore none of the usual clinical methods of examination in the presence of any indications for its use. The time demanded, therefore, in psychiatric work is considerable. In dispensary work time is limited, compromise is inevitable, and therefore the physician goes directly to those factors which experience leads him to consider the crucial factors in the individual case. This does not indicate a tendency to undervalue the rôle played by the simpler mechanisms in some types of mental disorder. It simply means that in certain cases experience has led the physician to lay most stress on the complex activities of the individual, and that it is in this sphere that he expects to find the factors which are open to modification.

To give as concrete as possible a picture of the actual work done in the dispensary, I should like to make a very summary review of 50 consecutive patients who were treated in the month of January. Of these 50 patients, 13 were children, 7 were adults with marked constitutional mental defects, 16 presented symptoms either of a recognized type of psychoneurosis or of a less well-defined invalidism, 4 were cases of dementia præcox, 5 had organic brain disorder, one had manic-depressive insanity, one patient was an epileptic, 2 were unclassified on the ground of insufficient data for diagnosis, chiefly on account of difficulty of language; in one case the symptoms did not go beyond the limits of a normal depression.

With regard to the cases of organic brain disease, 3 of these patients were taken into the clinic for further study and treatment. The cases of dementia præcox and of manic-depressive insanity were brought to the dispensary for the purpose of diagnosis and an outline of treatment.

The 13 children might be divided into 4 groups:

1. Children so seriously backward in their school progress as to be recognized as abnormal.

2. Children presenting marked defect of character accompanied by pronounced intellectual defect.

*Read at a meeting of the Baltimore City Medical Society, Feb. 6, 1914.

3. Children with psychoneurotic symptoms.

4. Children with pronounced speech defect.

With regard to the children with simple intellectual defect, the degree has always been estimated by the Binet-Simon scale. The etiological factors have been gone into and an attempt made to find out how far the defect could be attributed to ante-natal conditions, or to some organic lesion, either at childbirth, or during some infectious disorder of childhood. The family history of some cases has been investigated in a detailed manner by a special worker. The practical question with regard to such children is the extent of the further possible development in the individual case. Is the defect based on any remediable cause, is it only an apparent defect? Thus a child with a refractive error uncorrected, with headache, unable to maintain sustained attention, may fidget, annoy the others, become a source of annoyance to the teacher, get quite out of touch with the authorities, drift into the company of the really bad boys and develop habits impossible later to eradicate. Can the child be expected to become a wage-earning citizen and should its training have that in view, that is, should its training be along the lines of teaching in the ordinary grades, assuming that the ordinary school curriculum is a reasonable one? Or is the child never going to be a self-supporting social unit, will it always have to be safeguarded against exploitation, against becoming the tool of the unscrupulous, against becoming a disseminator of immorality?

Children with marked mental defect not based on remediable conditions require special training. The aim of this training should be correct conduct and the acquisition of mechanical ability, and not the general concepts of ordinary education. When the constitutional defect is not definitely recognized, the teacher is apt to apply misdirected energy, *e. g.*, to try to teach a boy of 8 or 9 years something which, with his defective equipment equal to that of a boy of 4 or 5 years, he is absolutely unable to grasp. Such children waterlog a class, impede the teaching of the more valuable scholars without conferring any compensatory advantage on the defective child. It is, therefore, important that the child should to a certain extent be standardized and his education have a direct reference to his actual capabilities. A satisfactory training of the child is the best guarantee of the later happiness of the individual. Unless the defect is recognized and proper measures taken, the child is apt to drift into bad company, develop criminal habits, and be a serious draw-back to the community. The danger of the exploitation of the female is obvious.

In many children, the general mental defect is accompanied by a variety of neurotic symptoms, and these children present extremely interesting problems. The psychoneuroses in the adult are only intelligible in the light of the development of the character of the individual, and in the children with neurotic symptoms one has the opportunity of studying at a very early stage developments which throw much light on the disorders of the adult.

The children are difficult to study under dispensary conditions. At first they are shy, uncommunicative, on the defense. Their visits are apt to be at rather long intervals, they are in a peculiar environment which does not elicit their characteristic reactions. Therefore one is frequently almost altogether dependent on the anamnesis. Here the social service department is able to give invaluable aid and to furnish a good idea of the actual environment of the child and of the remediable defects which it presents.

The following cases illustrate types of children dealt with:

Jan. 9, 1914. E. C. D., a boy of 7, is getting along very well at school, but during the last year has presented evidence of unstable equilibrium. The boy has bad dreams, and he has recently been stealing. The aunt considers that these symptoms came on after an operation for hernia last year, but the boy already had some difficulty with his instinctive life even before that. He had already been masturbating for about one year and he wet the bed until the age of six.

Remarks.—The case illustrates the frequent occurrence of fears and bad dreams in association with difficulties in the sexual life. It shows the importance of these fears as evidence of the advisability of helping the child in the sphere where help is apt to be refused. Scolding and punishment are apt merely to increase the tendency of the children to deal in a blind and evasive way with troubles which are almost inevitable in the course of development. The relation of stealing to the other difficulties of the patient has not been traced, but it is a symptom which must not be accepted as an irreducible defect of character, but as something which may be further analyzed and modified. It may be possible to help this boy by some educative talks and thus prevent the further development of an evasive way of dealing with his personal difficulties.

Jan. 17, 1914. A. A., a boy of 8½ years, had been pilfering for four or five months. The father dragged the boy to the clinic on the chance that the doctors might remove something from the boy's brain. At the consultation the boy was absolutely uncommunicative and frank relationships were not established. The father, disappointed at the impossibility of an operation, did not think it worth while to bring the boy back to the clinic. The social service worker made a home visit. She found that after each episode of pilfering, the boy was not punished physically, but was threatened and scolded to such purpose that for two or three days he was panic-stricken and in tears. The case presents a problem of very great importance, and the endeavor will be made to try and get into friendly relationship with the boy to see whether the stealing can be understood more clearly.

Jan. 9, 1914. C. E. D., a boy of 9½, whose mental age is 7½ years. The mental retardation is here due not to faulty environment or to a poor education, but to actual disease of the nervous system. The boy was a seven months child, had spasms at 18 months, frequent screaming spells until 5 years, and later, occasional attacks of a convulsive nature.

Remarks.—This case is one of a very large group of children who are brought to the dispensary, with a history of convulsive phenomena at some period of childhood. In some cases the disorder is in relation to more or less coarse damage to the brain, which appears to have been caused either by prenatal influences, difficulties of child-birth, or infective disorders in infancy. In other cases the patient presents no neurological symptoms except the convulsions, and the etiological factors are very obscure. From the point of view of treatment, these patients are of course very disappointing. They form an interesting material of study, for our knowledge of convulsive phenomena and the underlying conditions is extremely meagre.

Jan. 12, 1914. J. B., a boy of 14, during the winter of 1912-1913 began to stay in the house and made only desultory attempts to play or read. He showed a marked change of disposition and was quarrelsome with the other children. He would sit about in the house, fidgeting in his chair, smiling without cause. He became careless in his dress and as to personal cleanliness. At the same time he showed a compensatory fastidiousness with regard to eating. He would wash his dishes over and over before eating. He would refuse to eat things, saying that they were not clean. He was easily frightened, especially at night.

Remarks.—The case is evidently a rather serious one. The symptoms have no doubt to be partly understood in relation to the habit of masturbation, which had been learned from association with a gang of bad boys. The father spoke freely to the boy about it, but as a matter of fact the boy is rather afraid of his father.

Two cases may be referred to who have been coming to the dispensary for a considerable time:

May 24, 1913. M. S. is a queer, jerky little girl of 7 who is extremely fidgety, jumps about the room in a somewhat odd manner, is at times inattentive, asks questions as if she were rather stupid, and is apt to pretend that she does not know the nature of the place, the occupation of the doctor, etc. What is especially characteristic of this patient is her incessant asking of questions, many of which have quite obvious answers. Although the patient makes a superficial impression of being stupid, she is of normal intellectual level and her teacher finds her quite bright at school.

Remarks.—To understand the underlying forces and the mechanism of such a disorder is a difficult and tedious task, and is not made any easier by the infrequency of the visits to the dispensary. It is important to take this eager questioning of the child seriously, and to find out what are the main questions and what is the curiosity which thus expresses itself so indirectly. In this case the social service worker has visited the home regularly for a period of three months, and has been fortunate in establishing a very frank relationship. She has enabled the physician to understand the repressive atmosphere in which this child has been brought up and which put a strict taboo on many of the simple questions of the child. The mother expressed doubt to the social service worker as to whether she had done right in omitting to punish her 2½-year-old child, who had made some reference to his sister being in the toilet. The father was disturbed at the possibility of the patient being taught folk dances. "Is it necessary to ruin her soul in order to save her body?" The social worker has done what was possible in the way of advising the parents in matters of training and in the regulation of the habits of the child. She also conferred with the school teacher. The child was also taken into the Harriet Lane Home for a short period of observation.

May 21, 1913. W. S., a difficult boy of 12½ years, inattentive at school, unruly and bad-tempered at home, destructive and fond of teasing animals and children. The environment, however, was probably partly the cause of the boy's difficulties. The father punished the boy severely for every misdemeanor. After school hours he was obliged to study Hebrew with his father and had little time for amusement. The mental age of the boy was that of a child of 11 years. In school he was often punished, and on this account he disliked his teacher.

Remarks.—In this case a careful review of the whole situation with the parents was of great benefit and the boy reports to the dispensary regularly. The social service worker has obtained the intelligent cooperation of the family in the carrying out of the doctor's instructions as to a consistent home training. She has held monthly conferences with the school teacher whose latest report is that the patient's progress and general attitude are excellent. The boy has been brought into touch with a boy's club and gymnasium, where he is doing good work.

The social service department has also done a great deal for W. B., a boy of 11, who reports regularly at the dispensary. For some years he has shown choreiform movements. He is rather erratic in his behavior, fastidious in his food, disturbed in his sleep, afraid to sleep away from his parents. The boy was taught masturbation by comrades and treated improperly by an adult. For this latter episode he received a thrashing from his grandmother, which probably was the extent of the child's education as to how to deal with one of the most fundamental factors in his life. The combination of the symptoms in this case is a very common one, sleeplessness, disturbing dreams, fears, bed-wetting, masturbation.

Remarks.—In this case obviously the whole education of the child was at fault. The capriciousness of the child's eating and the irregularity of his hours were merely partial expressions of the result of a thoroughly faulty education. To deal with such a situation an efficient social service department is absolutely necessary. The worker has visited the family regularly, has instructed the parents in detail as to hygiene, has secured dental care for the patient, has given him a vacation in the country, has arranged for his admittance to the ungraded class and has talked with the principal and teacher as to his special needs.

Sixteen cases were grouped together, which presented either recognized types of psychoneurosis such as hysteria, or rather vague and ill-defined types of invalidism. It is not easy under dispensary conditions to do justice to such patients. The treatment involves the re-education of the patient, a tedious and difficult task.

The following cases may illustrate the problems presented by this group of patients:

Jan. 22, 1914. S. B., a young woman of 26, for several years had complained of a variety of symptoms, headache, hot flushes, burning sensations in her stomach, dizziness, sleeplessness, occasional nausea and vomiting. Apart from these symptoms, she said that she was quite happy, in fact the happiest woman on earth; this, notwithstanding the fact, later admitted, that she did not love her husband and still hankered after an old sweetheart whom she had discarded four years previously. The patient had been treated for several months. At first the symptoms were attributed to a hypothetical hyperthyroidism, but later it was concluded that all the symptoms were of psychogenic origin.

Remarks.—In such a case it is possible to let the patient understand much more clearly the relation of the symptoms to the underlying difficulties in her life. One still, however, has to face the unfortunate situation which the patient has created by marrying her husband on grounds of prudence, where her feelings were altogether with another man. Such a situation is a very important factor in perpetuating psychoneurotic symptoms once they are established.

Jan. 17, 1914. N. E. H., a young woman of 23, had recently passed through a brief semi-delirious episode, but now presented

only a vague nervousness with surface cheerfulness and conventional smile. In this case, too, the problem was to educate the patient in regard to those factors which had been dealt with very evasively, the semi-delirious episode itself being the disguised expression of factors repressed from her conscious life.

Jan. 28, 1914. B. K. M., a clergyman of 46, several months previously had had an attack of quasi-unconsciousness, since when he had complained of excessive fatigue. Nineteen years previously he had had a nervous attack which his physicians said bordered on St. Vitus' Dance. The very fact that he had become a clergyman was to a certain extent a compensation for difficulties not squarely met. He had given up another occupation to enter the ministry, and one year later he had the involuntary movements referred to above. In the third year of the ministry he had a worse break-down. Nine years later he had an attack of shortness of breath, palpitation, marked anxiety, disturbing dreams of the nature of nightmare.

Remarks.—Even in a single interview it was possible to see in outline the mechanism of the disorder, and to put this before the patient. The amount of insight thus acquired by the patient along with the reassurances given him seemed to be decidedly helpful. Such a case, however, requires rather prolonged treatment, and the patient did not live in Baltimore. The case was gone over with the family physician who accompanied him, and the patient was recommended to go over with his physician in very much greater detail the main points which had been only partly reviewed during the consultation.

The following cases represent a type very familiar in dispensary work, so familiar as to have lost much of its interest for many physicians. Although familiar with these cases, we are, however, far from understanding them and they present problems of very great psychiatric interest.

Jan. 20, 1914. H. G. is a very typical example of this group of patients. She is a woman of 39, very unhappily married, who says that she is tortured by her husband, that he makes her sick, that she only wishes to live for her children. The patient complains of a variety of somatic symptoms, pain in the head, tightness in the chest, pain in the abdomen, but a thorough physical examination reveals nothing to account for her bodily symptoms.

Remarks.—The patient's invalidism appeared to be in close relation to her general unhappy situation. She had, however, not reacted with the special symptoms of a hysteria nor another psychoneurosis. This type of invalidism is partly intelligible as a reaction to the definite situation; to a certain extent it affords protection from the demands of the environment and brings in certain immunities and privileges. It might best be described as a "situation-neurosis." The importance of the formulation in this term is that we keep before us the practical problem of seeing whether after all the situation may not be advantageously modified, so that we do not confine ourselves absolutely to dealing with the patient as an isolated unit. At the same time it is important to encourage the patient to face frankly the difficulties of the situation and to realize the presence of internal obstacles of which she was previously ignorant. We thus try to improve the adjustment of the patient at whatever point we find available for modification. It is probable that in this case the patient had never in her life reached a satisfactory level of independent activity. As a child she had been wrapped up in her mother, and after the death of her mother she said that she had cried a whole year. The analysis of the development of her character and of the circumstances which led to her unsatisfactory marriage would probably have thrown some light on the later development of invalidism, which after all represented a rather childish type of reaction.

Jan. 27, 1914. A. A., a Hebrew woman of 38, complained fluently and continuously of innumerable pains. She clamored for sympathy. She knew that the hospital doctors could not help her, but she could not stay away from them. Whenever she was taken into a hospital, her condition changed entirely and she was well in a couple of days, but she relapsed after her discharge. In this case the same problems are brought up as in the previous one.

Jan. 16, 1914. J. B., a woman of 40, after some trouble with her neighbors, became nervous, sleepless and suffered from headaches. Her complaints found little sympathy with her husband who had been nagging her ever since her marriage 17 years ago. She had been in one hospital, but left after one week, as she was disgusted with the treatment.

Remarks.—In this case we see how an illiterate woman, unhappy with her husband, in the face of additional difficulties in life, falls back on a variety of mild complaints which relieve her of some of her responsibility and throw it on society. It is very difficult in an illiterate patient of this type to do much in the way of getting her to understand the true nature of the trouble, as an inferior adaptation to the actual situation. It is difficult enough with an educated woman of the same age.

It is interesting to notice the percentage of Russian Hebrews in this group. This type of disorder is probably closely related to the racial character and to the special difficulties in the life of immigrants of this class.

The above very summary review may serve to indicate the actual problems dealt with in the dispensary; these problems are not only of great psychiatric interest, but touch many vital interests of the community. They raise important social and educational issues, and it is hoped that even where in the individual case little can be done, the thorough study of the disorder in its complete setting may contribute data of value in relation to the mental hygiene of the community.

DYSTROPHIA EPITHELIALIS CORNEÆ: REPORT OF A CASE.*

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The patient, a negro, 53 years of age, married, and a whitewasher by occupation, came to the clinic on June 9, 1913, complaining that, for several weeks prior to that date, there had been a gradual diminution in the vision of his right eye, unaccompanied by pain. There seemed to be a "shadow" before his eye, and for the past week it had been slightly sore.

*From the clinic of Dr. Samuel Theobald, Baltimore Eye, Ear and Throat Hospital.

Previous medical history negative; no malaria, no trauma, no syphilis. Gross inspection revealed a well-nourished, vigorous man with a rather dry, coarse skin, and a coated tongue, but, on the whole, presenting no abnormal appearance.

Minute inspection of the cornea of the right eye, with the binocular loupe, showed a small, central, superficial, herpetic, epithelial loss, which was clear, uninfiltrated, and stained faintly with fluorescein. Midway between the center of the cornea and the limbus a very faint, whitish crescent was seen, evidently lying between the epithelium and Bowman's membrane, or in the anterior lamellæ of the substantia propria. The corneal epithelium, itself, surrounding this area and extending to within about 3 mm. of the limbus, was diffusely clouded and hazy, as though œdematous, minute distinct vesicles being present. There was only slight congestion of the ciliary vessels and the iris was normal in appearance, although the pupillary reactions were sluggish. The tension of the globe was not elevated, and the anterior chamber was not shallowed. No view of the fundus could be obtained with the ophthalmoscope, and vision was limited to counting fingers at 40 cm.

The observer's first thought was of a rare, ring-shaped keratitis, which was somewhat borne out by the fact that the crescent later completely encircled the center of the cornea. However the inflammatory evidences, excluding the vague pericorneal congestion, were so slight, and so out of proportion to the corneal disturbances, that one felt inclined to abandon the diagnosis of an actual keratitis and look upon the condition as a trophic or nutritional affection, an epithelial dystrophy, due, perhaps, to some general dyscrasia, a view which was partially substantiated by finding diminished sensibility of that cornea as compared with its fellow, both being hypo-normal in that respect.

The patient was advised to enter the hospital, and the following examinations were made by Dr. Guerinot:

Neurological and physical—negative.

Blood: Pale, slowly coagulable, little fibrin, Hb. 68%, R. B. C. 3,650,000, W. B. C. 6200.

Differential count: Small mononuclears 24%, large mononuclears 4%, polymorphonuclears 70%, eosinophiles 2%.

Blood pressure, 148 mm.

Tuberculin test (von Pirquet), negative.

Wassermann blood test, negative.

The patient was placed under an appropriate local and general regimen with no appreciable change in the corneal condition, until June 24, when urinalysis showed a specific gravity of 1030, and 0.5% sugar. A strict "sugar free" diet was at once ordered; in six days there was a complete restoration of the corneal epithelium, and on June 30 the patient was discharged and told to report at regular intervals for treatment in the dispensary.

He failed to do so, however, and did not come back until August 18 when he returned to the clinic with the haziness of the cornea much deeper, more diffusely located, and amounting to a positive stippling—giving the epithelium a roughened appearance, as of glass which had been breathed upon.

It is interesting to note, in this connection, that on an intervening and unrecorded occasion, the man returned to the dispensary with a foreign body impacted upon the diseased cornea. My colleague, who was in charge at the time, upon brushing off the particle with a cotton-wound spud, noticed that the hazy epithelium at that situation was wiped away also, leaving clear substantia propria beneath. This demonstrates how superficial was the œdema.

Upon his return, in addition to an increase in the œdema, there was a large, central, bullous loss of epithelium, deeper than the first, and staining markedly with fluorescein. The whitish ring was more pronounced.

He was promptly re-admitted, and again placed upon a rigid sugar free diet, close questioning having revealed the fact that he had been partaking freely and indiscriminately of starch-containing foods. The same local and general treatment was ordered as on the previous visit.

On this occasion a slight transitory hypertony was several times noticed, although ophthalmo-tonometry was not resorted to, because of the epithelial disturbances. In fact, the epithelium did not respond to therapeutic and dietetic measures as rapidly as before, and complete restoration did not occur for 18 days. This time the patient complained, once or twice, of slight local pain, which was promptly relieved by instillations of a 1% holocain hydrochlorid solution.

On September 8 he was again discharged from the hospital with the corneal haziness much less marked, while a very dim, undetailed view of the fundus could, for the first time, be obtained with the ophthalmoscope. His vision, 4/100, also showed great improvement. Urinalysis gave a high specific gravity—1031, but no sugar, acetone, or diacetic acid. In this connection, let it be noted that, while the diet caused a loss of weight, and less healthy general appearance, the corneal disturbance was steadily ameliorated thereby.

He was next seen on October 10, when his vision had improved to 20/120, and the œdematous haze of the cornea had cleared markedly. The iris was clearly visible, but the white ring was still present, while the corneal apex was marked by a small, almost circular, opaque spot, the site of the previous tissue loss.

Four days later, however, when he brought a 24-hour specimen of urine to Dr. Guerinot, 2% sugar was found, in conjunction with a specific gravity of 1032, although there were no decomposition products such as acetone or diacetic acid.

Strict dietary instructions were again given him, and he was told to instil 5% dionin collyrium locally, each day, in order to stimulate the nutrition of the cornea.

The man was last observed on October 31 when the cloudiness had diminished greatly, but below the corneal center, and above the white ring, a small bulla had formed, evidently containing a clear liquid. This was directly beneath the epithelium and moved in any direction when pressure was made against it through the lower lid. Vision had fallen slightly, being 20/160 + +, although a 2.25 diopter convex sphere, tried for the first time, brought it to 20/50.

In a rather careful survey of the literature upon the subject of corneal dystrophies, the writer has been unable to discover a single reported case with diabetes as either the exciting or indirect cause. In fact, those who have reported the condition, Fuchs, Paul Knapp, Troncoso and Reese, have consistently failed to detect any definite ætiological factor whatever. They agree, however, in almost all of the following points: that dystrophia epithelialis corneæ occurs most frequently in middle life, that it usually affects the female sex, with a predisposition for the right eye, that it is frequently associated with slight and transitory rises in the intraocular tension, and, finally, that the course of the degeneration, as well as the visual diminution, is gradually progressive, despite any known form of treatment.

The condition, as such, was unknown until 1910, when Fuchs' interesting monograph appeared, describing the 13 cases he had seen since 1900. As he says, many cases, prior to that time, had undoubtedly been diagnosed and treated as glaucoma, owing to the elevation of intraocular tension, and the almost characteristic appearance of the corneal epithelium. Since his splendid description of the course and character of the condition, however, several observers have diagnosed

similar cases, and added their reports to the literature upon the subject, a total of 17 cases.

The slow and progressive course of this condition distinguishes it clinically from any of the inflammations, for the latter are marked by a period of progression, followed later by one of regression, while anatomically the dystrophies are characterized by degenerative changes as opposed to the cellular invasion of inflammatory lesions.

The majority of dystrophies are the expression, either of a local disturbance of nutrition, or, as Reese has pointed out, some general malnutrition; for example: the deposits of mucin in myxœdematous subjects after thyroidectomy, the grayish-green discoloration of the cornea occurring in disseminated sclerosis, and, according to Weeks, disease of the Gasserian ganglion and traumatism. (A physiological parallel to the dystrophies is found in the familiar "arcus senilis.") But, to dystrophy of the corneal epithelium no definite ætiological factor has been ascribed. Hence the writer feels some hesitancy in advancing his opinion that diabetes was the direct or remote cause in the case which has just been reported, even though the diet and presence or absence of sugar did so markedly influence the ocular condition.

If the metabolic disease in question did bear some definite relation to the trophic disturbances which took place in the cornea, some interesting conjectures as to the *modus operandi* might be made. Was the process caused by a direct toxic action on the trophic apparatus, for instance, by a temporary flooding of the blood or lymph with diacetic acid or beta-oxybutyric acid? Or was the degeneration purely a nutritive one caused by a perversion of the pabulum normally carried to the corneal epithelium, and due to a degeneration in the walls of the small blood vessels? Again, might the bullous condition of the epithelium to analogous to the desquamative dermatitis so constantly observed in diabetes?

Epithelial dystrophy is easily differentiated from Family Nodular Keratitis, from affections due to noxious vapors, from keratitis vasculosa with herpes, from post-operative sclerosis, and from hyaline or fatty degeneration of the cornea.

The case just reported resembled those of Fuchs in that it was associated with transitory periods of hypertony, and, somewhat one described by Reese with a bulla in the center of the opaque cornea. It makes the third reported case associated with pericorneal injection.

The pathology of dystrophia epithelialis corneæ is rather vague: Paul Knapp contends that it is due to an œdema of the epithelium. Fuchs has had the opportunity of making a microscopical examination of one case. There was grayish opacity and roughening of the surface of the cornea from small vacuoles in the epithelial cells, and *newly formed tissue between Bowman's membrane and the epithelium.* This tissue is homogeneous, and without signs of hyaline or mucoid degeneration. The epithelium covering it is thinner than normal, but the cells are not flattened or hornified. He thinks that in the earlier stages the epithelium is probably thickened and vacuolated.

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LOUIS HÉBERT.*

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Every student of Canadian history knows that from the first days of the colonization of New France, an important rôle as colonists was played by members of the medical profession. If they were not remarkable for any great professional brilliancy, they were generally men of sterling character and courage. Louis Hébert, apothecary, surgeon, and agriculturist, is regarded, next to Champlain, as the "Father of New France." When Champlain induced his old friend of Port Royal to venture once more to become a colonist of New France, he knew he had accomplished a greater work in building up his colony than had been done since its foundation. For Louis Hébert had proved his worth at Port Royal, not only as a surgeon, but as a keen and ardent agriculturist.

When Champlain returned to France in 1617, his mind filled with the wondrous future he was planning for Quebec, he knew it was of vital import to obtain as colonists men of the best type, not jail-birds, as Roberval had had to contend with, nor mere adventurers, who came for the love of adventure or gain, and went away again, but men who would cultivate the land. And so the thought of his friend came to him —Louis Hébert, who had cultivated such beautiful gardens at Port Royal, until that settlement was destroyed by Samuel Argall, when Hébert returned to France.

Louis Hébert had received a good education, for his father was a man of repute, being apothecary to Catherine de Médicis. Louis followed his father's business and had a shop on the banks of the Seine, where he was well patronized. But in the summer of 1606, he suddenly announced to his friends and relations that he was sailing with Poutrincourt and fifty other colonists for the New World, of which there had lately been so much talk. Among others who sailed in the ship was a Parisian lawyer, historian, and poet named Lescarbot, the friend and lawyer of Poutrincourt. It is to Lescarbot we are indebted for the vivid portrayal of how the first winter in the new settlement at Port Royal was passed. "For my part," writes Lescarbot, "I can say that I never worked so hard in

* Presented by Dr. Henry M. Hurd at the meeting of The Johns Hopkins Historical Society, March 9, 1914.

my life. I took pleasure in laying out and cultivating my gardens, in making alleys, building summer houses, growing wheat, rye, barley, oats, beans, peas, and garden plants, and in watering them, for I was most anxious to find out, by personal experience, the quality of the soil."

With Lescarbot worked Hébert and the days were not long enough for these two enthusiastic agriculturists: they must needs work by moonlight, digging and planting. Lescarbot and Hébert returned to Paris in the autumn of 1607, but Hébert, after a short stay, came back to Port Royal accompanied by Biencourt, Poutrincourt's son. He assisted Biencourt in managing and taking care of those colonists who had remained, and when Biencourt was absent, acted as his lieutenant until the place was destroyed in 1613, by the English. Hébert then returned to Paris as he thought, for good, and once more opened his shop on the banks of the Seine.

When Champlain arrived in France in 1617, he visited Hébert, and so beguiled him with his marvellous accounts of the country about Quebec that Hébert again sold his possessions and with his family started for Honfleur, where he arrived on March 14. Champlain had induced a new fur trading company to promise to support Hébert and his family for two years, and afterwards to make him an allowance of two hundred crowns for three years.

On arriving at Honfleur, Hébert found, to his chagrin and dismay, that all the promises which the company had held out to him were false. In vain did Hébert appeal for fair treatment. The company refused to keep their promises; they offered him one hundred crowns instead of two hundred, and, moreover, required his bond for free medical attendance at all times to the settlers and to the clerks belonging to their company. Hébert was at their mercy, but rather than return to Paris, for he had disposed of all his effects, he embarked with his family for the New World.

Their passage was a stormy one, and when they reached Newfoundland, the ship encountered a great field of ice-bergs. At one time, it seemed as if all on board must perish. Father Joseph, one of the passengers, knelt upon the deck and prayed for Divine assistance, and we are told in the "Relations of the Jesuits" that Madame Hébert took Marie Rollet, her youngest child, and held her up through the hatchway, so that she might receive the father's blessing. It was on this long and stormy voyage of thirteen weeks and a day that the courtship of Anne, the eldest daughter of Hébert, commenced. Among the passengers was one Etienne Jonquest, a sturdy son of Normandy. He wooed Anne so successfully that the two were married in the autumn by Father le Caron. This was the first marriage in Canada according to Church rites, but Anne had a short wedded life, for she died in 1619 and was followed by her husband within a few weeks.*

*Thus we have mention of the first marriage in New France, and in connection with that it is interesting to notice the first marriage in New England took place the 12th of May, 1617, two months and a half earlier, between Edward Winslow and Susannah White.

The passengers were first landed at Tadousac June 14, and after returning thanks for their safe arrival, they went on to Quebec.

Quebec consisted at this time of a few roughly-built huts, clustered close to the water's edge; they were inhabited by clerks, interpreters, and others employed by the company.

Louis Hébert chose for the site of his future home, land on the height above—later called Mountain Hill, part of which was between the present streets of Famille and Couillard. He lost no time in building his home, a substantial stone house, thirty-eight feet in length by nineteen in width, the best house for many years to come in Quebec, and the first dwelling in what was afterwards the Upper Town, for as yet Champlain had not built his fort on the cliff. Not far from the house ran a stream of pure water, and this had decided Hébert in his choice of a site. For ten years Hébert toiled like any hardy peasant upon his farm. He sowed Indian corn and vegetable seeds, planted apple trees and his beloved grape vines. All his spare time, when not attending to the sick, was devoted to his agricultural pursuits. Every year he cleared more ground and tried fresh experiments in farming; every year his farm grew more and more productive. He was able, almost from the first, to support his family on what he raised, and this in spite of the fact that the company forced him to sell them his grain at a price fixed by themselves, one of the many acts of injustice rendered him by the company. This farm was the show farm of Quebec—the model farm, so to speak, of the day. From this time agriculture began to find its place in New France, and in these golden days of Canada's greatness, she may well be proud of her first farmer.

It is claimed that the first seignory mentioned in the records was that of Sault-au-Matelot near Quebec, which was ceded to Louis Hébert by the duc de Montmorency in 1623 and that this was added to three years later by the duc de Ventadour of the fief of d'Epinay on the St. Charles River. A controversy has arisen, however, as to whether Hébert may be rightly called the first seigneur in New France.

The life of this clever, original Frenchman was crowded with interest, from the day he first left Paris and settled at Port Royal to his final home at Quebec. Through innumerable hardships and difficulties he had struggled on with unfailing courage and hope. He had accomplished wonders during his ten years' residence at Quebec. In January, 1627, a great sorrow came upon his friends. Hébert fell on the ice when he was crossing a river and died shortly afterwards from the effects of the fall. They buried him amidst great grief in the cemetery of the Recollet Fathers at the foot of the cross. Only three days before his accident, Hébert had visited the Fathers and as though he had had a premonition of his death, he had requested that when that event took place, he should be buried in that spot.

It is supposed that the first time a notary's services were required in New France was in the drawing up of Hébert's will.

Among the settlers who had remained at the advice of

Champlain, when Kirke captured Quebec, were the Hébert and Couillard families, as well as a surgeon, Adrien Duchesne and his wife, who came to Quebec in 1618. Duchesne was the second medical man to settle there.

When Champlain returned to Quebec after the treaty of St. Germain-en-Laye, he was accompanied by Fathers Paul le Jeune and Anne de la Nouë. They went immediately to Madame Hébert's house, the only one spared in that scene of desolation. Here Madame Hébert lived with her second daughter, Guillemette and her son-in-law, Guillaume Couillard. Couillard had come to Quebec in 1613 as a carpenter. But he had soon become, under Louis Hébert's teaching, an active farmer. In 1628, instead of tilling the ground by hand, oxen were used, and so well had Couillard managed Hébert's farm that it was spoken of as the one fertile spot at Quebec when Champlain returned.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

December 15, 1913.

A Case of Infection with *Agchylostoma duodenale* Treated with Oil of Chenopcdium (with Demonstration of Specimens). DR. ROBERT L. LEVY.

The patient, a Norwegian sailor, aged 23, was admitted to the Johns Hopkins Hospital eight weeks ago, complaining of headache, general bodily pains and swelling of his legs. He had always been strong and a hard worker, and had sailed to almost all parts of the civilized world. The present illness began in Mexico one month before admission here. There, for the first time in the course of his wanderings, he went about barefoot. He soon developed a painful sore on the dorsum of the left foot, which discharged and resisted all efforts made to heal it. He noticed no itching of the foot. Shortly afterward the feet and legs began to swell and the patient felt weak, irritable and incapable of work. He went to a hospital in Mexico and remained there three weeks; during this time he was given no medicine. The swelling of his legs, however, disappeared and he was discharged somewhat improved. Twelve days before admission here his legs again began to swell, he felt feverish and weak, and there was moderate diarrhœa, so he boarded a ship for this country and landed in Baltimore.

On admission there was striking pallor, fever, tachycardia, brawny œdema of ankles and lower legs and a pigmented scar on the dorsum of the left foot. He was extremely weak and very irritable. The blood showed 1,660,000 red cells, 6,440 white cells and a hæmoglobin of 25% (Sahli). In addition, there were seen many hyaline and crescent forms of æstivo-autumnal malaria. An examination of the stools revealed the ova of *Trichuris trichiura* and of the hookworm.

The malarial infection was soon gotten under control. The whip worm ova spontaneously disappeared from the stools following vigorous purgation, but the usual medication with thymol, as recommended by the Porto Rican Commission, failed to get rid of the uncinaria, though thrice repeated at one week intervals.

Accordingly, our patient was given the oil of chenopodium according to the directions (slightly modified) of Schüffner and Verwoort (München. med. Wchnschr., 1913, LX, 129). The patient was starved for eight hours, at the end of which period he was given an ounce of Epsom salts. Two hours later, 16 drops of the oil of chenopodium on a teaspoonful of granulated sugar were administered. This dose was repeated at two-hour intervals until three doses had been given. Two hours after the last dose of chenopodium the patient was given an ounce of castor oil and 50 minims of chloroform. On sifting the stools collected during the next 24 hours, 19 hookworms of the Old World type were found. Ova continued to be discharged in the fæces. On repeating the treatment five days later, seven more hookworms were expelled, and this time no ova could subsequently be demonstrated in the stools. However, another course of chenopodium was given to be sure that no parasites remained; none were expelled. The stools have since been free from ova, and I believe we may consider the patient cured of his intestinal parasitism. He has gained 30 pounds in weight. The blood now shows:

R. B. C., 4,110,000; W. B. C., 11,000; Hb. (Sahli), 70%. It is of interest that whereas on admission the eosinophiles formed but 7% of the white cells, there is now an eosinophilia of 36%. Such a rise in eosinophile cells the Porto Rican Commission regards as of good prognostic import.

As compared with thymol as a vermifuge in uncinariasis, oil of chenopodium seems to offer certain very definite advantages:

1. According to Schüffner and Verwoort it is more efficacious.
2. It is not unpleasant to take.
3. Its ingestion is not accompanied by any disagreeable after-effects. In a recent article Stiles and Boatwright have pointed out that unpleasant symptoms appeared in over half of a large series of cases treated with thymol, and carefully observed to determine this very point.
4. In therapeutic doses it is non-toxic. Thymol occasionally, though rarely, produces symptoms of serious intoxication.

NOTES ON NEW BOOKS.

In Memoriam: Dr. James Livingston Thompson, Dr. Daniel A. Thompson. (*Indianapolis, Indiana, The Hollenbeck Press, 1913.*)

This small volume is a collection of pleasant and fitting tributes to these two noteworthy practitioners of Indianapolis. They were both men of mark; but many fine men like them pass away, and their work and names are soon forgotten, for they are uncommemorated, and so such "In Memoriam" tributes are always precious records in the history of the medical profession. All friends of these two doctors will be grateful to see these warm expressions of affection and esteem thus perpetually recorded.

Surgery of the Upper Abdomen. By JOHN B. DEAVER, M. D., etc., and ASTLEY PASTON COOPER ASHHURST, M. D. Vol. II. Illustrated. $5. (*Philadelphia: P. Blackiston's Son & Co., 1914.*)

It is more than four years since the first volume of this excellent surgery appeared, but the wait is compensated for by the thoroughness and completeness of the second and last volume. The authors have carefully studied the great amount of literature on the subjects treated—gall bladder, liver, pancreas and spleen—and their work is one that all surgeons will be glad to own. Their reputation gives weight to their words, and the lists of references make it easy for the reader to look up original articles. The now

completed "Surgery of the Upper Abdomen" is an important contribution by American authors to the literature of surgery, and will bring them well won repute by foreign students of the subject.

C. Merck's Annual Report, 1912. Volume XXVI. (*Darmstadt, C. Merck, Chemical Works, 1913.*)

Pharmacologists especially, and those who teach therapeutics, will find in this volume much valuable information on the newest remedies. The work is reliable, carefully prepared from the best authorities, and is conveniently arranged. The physician, at a loss for some new remedy, can easily secure one for almost any disease and symptom from this list, and can use it with safety if he follows the directions given.

Science and Education: A Series of Volumes for the Promotion of Scientific Research and Educational Progress. Edited by J. MCKEEN CATTELL. Volume II. *Medical Research and Education.* By RICHARD M. PEARCE, WILLIAM H. WELCH, W. H. HOWELL, FRANKLIN P. MALL, LEWELLYS F. BARKER, CHARLES S. MINOT, W. B. CANNON, W. T. COUNCILMAN, THEOBALD SMITH, G. N. STEWART, C. M. JACKSON, E. P. LYON, JAMES B. HERRICK, JOHN M. DODSON, C. R. BARDEEN, W. OPHÜLS, S. J. MELTZER, JAMES EWING, W. W. KEEN, HENRY H. DONALDSON, the late C. A. HERTER and the late HENRY P. BOWDITCH. (*New York and Garrison, N. Y., The Science Press, 1913.*)

The basis of this handsome book of 536 pages seems to be the five Hitchcock Lectures delivered at the University of California in 1912 by Prof. R. M. Pearce, of Philadelphia (originally published in *Popular Science Monthly*), which cover 88 pages; the remainder of the book consists wholly of papers published during the past twenty years in various medical and scientific journals. They all represent different strata of thought during the period mentioned and consequently at the present time possess very different values. Some of the issues discussed have passed into history and have given place to new ideas and suggestions which a decade ago would have seemed subversive of proper conceptions of medical education.

The most interesting of Prof. Pearce's lectures relates to problems in immunology, protozoology, chemotherapy, physiological chemistry, experimental pharmacology and experimental pathology, in which he gives an admirable review of the studies in immunity which were initiated by Behring and Kitasato, and later led to the diphtheria antitoxin of Behring and Knorr; the antibacterial sera of Ehrlich; the opsonins of Wright; the practice of immunizing vaccinations as now best illustrated in typhoid fever; the Wasserman test by fixation of complement; the condition of increased susceptibility known as anaphylaxis; the study of filterable or ultramicroscopic viruses by Flexner and their relations to epidemic poliomyelitis.

In protozoology he speaks of the discovery of the first protozoon definitely associated with disease in man in 1860 and known in 1875 to be the cause of amebic dysentery; of the discovery of the *plasmodium malariæ* by Laveran in 1880 which settled definitely the cause of malarial fever; of the discovery of the cause of Texas fever in 1893 and its mode of transmission by Smith and Kilbourne, which had important influence subsequently on the study of the transmission of malaria and yellow fever, sleeping sickness and other diseases due to pathogenic protozoa. This admirable review is followed by a review of the wonderful work of Ehrlich in devising a method of combating protozoan diseases by direct toxic agencies to destroy the specific protozoon; and of the discovery of salvarsan to destroy the spirochetes of syphilis. He believes that "with a record of about a dozen drugs which can be used to cure or modify disease caused by nearly a dozen different protozoa, chemotherapy offers promise of results which with serum therapy and vaccination in bacterial diseases will sharply limit the ravages of the transmissible diseases of man and animals." In the same lecture he traces the growth of physiological chemistry in its investigation of problems of digestion metabolism and secretion in health and disease to ascertain better the mechanism of cell activity and the interrelation of the functions of cells in different parts of the body. His references to experimental pharmacology, experimental pathology and experimental physiology, although much less extended, are full of interest. The whole series of five lectures is of unusual value and should go into the hands of all medical students. They bring into compact form the methods and results of medical research and point out suggestive means of further study.

The succeeding papers as already intimated are of varying interest, but all are valuable contributions to many important branches of medical education. Occasionally, as in Councilman's "Experiences of a Medical Teacher," especially in a conspicuous foot-note on optimism, we get a refreshing vein of characteristic cynicism. The enterprise of the industrious editor of the series is worthy of all praise. It is to be hoped that the succeeding volume on "University Control" may be presented upon a similar plane of high idealism. The whole situation calls for a much less personal attitude than has characterized the majority of writers upon it.

Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. 1/9. (*Calcutta: Superintendent Government Printing, India, 1913.*) *No. 60* (*New Series*).

Studies on the Mouth Parts and Sucking Apparatus of the Blood-Sucking Diptera.

No. 4. The Comparative Anatomy of the Proboscis in the Blood-Sucking Muscidæ. By CAPTAIN F. W. CRAGG, M. D.

For a small class of specialists these reports of Captain Craggs are of real interest and importance. This is the fourth of his most exhaustive papers. All are accompanied by excellent drawings, and are valuable contributions to the anatomy of disease-producing insects.

Diseases and Deformities of the Foot. By JOHN JOSEPH NUTT, M. D. Illustrated. $2.75. (*New York: C. B. Treat & Co., 1913.*)

The author says in his preface that this book is intended for those who have not made a special study of orthopedics. But is the average practitioner capable of treating the simpler deformities of the feet with such a brief work as this to guide him? We do not think so, and feel that these deformities should, whenever possible, be referred to the specialist. The best orthopedists frequently fail to secure good results in these operations, and a bungling operation only makes the condition harder to treat and cure. The very lack of details in a short treatise of this nature makes it unsuited to the needs of one ignorant of the subject, who if he wants to treat a club foot, should get all the information he can as to how to operate before attempting to correct the deformity, and not rely on a well-drawn outline sketch, such as this is.

Burdett's Hospitals and Charities for 1914. Being the Year Book of Philanthropy and the Hospital Annual. By SIR HENRY BURDETT, K. C. B., K. C. V. O. Twenty-fifth year. (*London: The Scientific Press Limited, 28 and 29 Southampton St., Strand, W. C.*)

The present issue of Hospitals and Charities is styled in an interesting preface, the Silver Jubilee Volume, because of the completion of the twenty-fifth year of continuous publication. To those who saw the early volumes the development of the work during the past few years is a matter of surprise and gratification.

We are told that the volume for 1914 contains accurate figures from the audited accounts of six thousand distinct institutions for the year ending December 31, 1912. No person who has not wrestled with the intricate statistics of a single hospital can adequately appreciate the immense labor involved in this annual review of the statistics of charity and philanthropy.

In addition to these statistical reviews of the operations of hospitals we find interesting accounts of several distinctive British organizations to foster and extend their work, such as "The King's Fund and the League of Mercy," "Hospital Sunday" and "Hospital Saturday." The apparent decline of the Hospital Sunday movement which seems to require each year a larger subvention from legacies and interest from invested funds seems difficult of explanation. In the United States the observance of Hospital Sunday was a direct importation from England, and as it did not grow out of any popular feeling, it is not strange that it has never had any adequate support, and outside of two or three large cities we now hear little about it. In England, however, it was wholly different. It is possible that "The King's Fund and League of Mercy" tended to draw away its supporters among the upper classes; and "Hospital Saturday" its friends in the laboring classes.

The comparative tables of the cost of nursing in the London and Provincial Hospitals respectively are full of interest. The cost of nurses, *per head*, to use the editor's phrase, in London in 1912 varied from fifty-four pounds at St. Bartholomew's to thirty-nine pounds eight shillings at Guy's; and outside of London from forty-three pounds six shillings at the Glasgow Royal Infirmary to thirty-two pounds eight shillings at the Dundee Royal Infirmary. A strong plea is made for more definite systems of accounting in every Nurses' Training School in order to determine the exact cost of maintenance. It is suggested that separate accounts be kept of every item of support, even where the Nurses' Home does not possess a separate kitchen. A separate kitchen requisiton sheet is further suggested for each and every department of a hospital so that it may be shown what sums are expended for food, etc., per person upon the medical staff, the nursing staff, the employes and the patients. The practice of lumping together such expenditures to secure an average daily cost of support of all persons residing in the hospital irrespective of the varying circumstances and cost of maintenance is justly deprecated.

In view of the comparatively small number of convalescent hospitals or homes in America it is of interest to note that three hundred such institutions are to be found in the United Kingdom alone. It is evident that we need a much larger number.

The financial details of the expenditures of hospitals in Great Britain and America are thoroughly analyzed and deserve careful study by all hospital officers. It is to be regretted that comparatively few hospitals of the United States are thus reported because of the lack of uniform systems of recording expenditures. The leading hospitals of English-speaking countries owe it to themselves to agree at an early day upon a form of comparable statistics.

Bovine Tuberculosis and Its Control. By VERANUS ALVA MOORE, M. D., etc. $2. (*Ithaca, N. Y.: Carpenter & Co., 1913.*)

Now that the subject of tuberculosis has gained a widespread attention, this book should find a large and interested public; for tuberculosis in cattle has assumed an integral and important part in the broad plan for suppressing the disease. It touches human pathology and hygiene, invades sociology and encloses pressing economic questions. In simple form Dr. Moore gives the essentials about bovine tuberculosis. The information is not exhaustive, but it is in general accurate and it is an advantage that the book is perfectly intelligible to intelligent laymen.

Disputed questions are treated with moderation and conservatively, especially for instance, the chapter on the value of tuberculin in diagnosis. The methods of eliminating tuberculosis from herds are given full consideration. Those interested in the establishment and maintenance of sanitary dairies should find the book invaluable.

Modern Problems in Psychiatry.. By ERNESTO LUGARO. Translated by DAVID ORR, M. D., and R. G. ROWS, M. D. With a foreword by SIR T. S. CLOUSTON, M. D., LL.D. $2.50. (*Manchester University Press, 1913.*)

The first edition of this work was published in 1909. No radical alteration has been made in this edition. The book is one which enjoys a well-deserved popularity owing to the clearness with which some of the more general problems in psychiatry are discussed, but on the other hand some of the more modern problems are practically not touched upon. According to Clouston, however, who writes a foreword to the book, Lugaro has pointed out future lines of research more clearly and fully than almost any of the modern authors.

In the general introduction the relation of psychiatry to general medicine is discussed, and the importance of welding it with general clinical medicine is strongly emphasized. Chapters are devoted to the psychological problems, the anatomical problems, pathogenesis, etiological problems, nosological problems, and practical problems.

Throughout his work Lugaro discounts the importance of psychic causes in the etiology of mental disorders, and his somewhat formal point of view may be seen from the fact that of all factors he regards them as being the most insignificant.

Ophthalmic Diagnosis. By DR. C. ADAM, Berlin. Translated by M. L. FOSTER, M. D. Illustrated. (*New York: Rebman Company, 1913.*)

This is probably one of the best, if not the best, atlas of the internal diseases of the eye which has ever appeared. Not only are the pictures well nigh perfect, exhibiting the minutest changes in practically every disease, and altered condition of the fundus oculi met with, but the descriptions accompanying the same not only describe the plates, but furnish a wealth of accurate clinical and pathological information. The cases shown have been so carefully worked up and described that we regret that the author has not inserted the possible vision which each case had in every instance, while suffering with the pictured eye lesion. This would have made this work incomparable as a work of reference in medical-legal and court questions, as far as the internal lesions of the eye are concerned. This book deserves to be held in the highest esteem by all medical men.

Surgery of the Eye: A Hand-book for Students and Practitioners. By ERVIN TÖRÖK, M. D., and GERALD H. GROUT, M. D. Illustrated. $4.50. (*Philadelphia and New York: Lea & Febiger, Publishers, 1913.*)

There is nothing particularly new or novel in this work, nor are the operations described more accurately or better than in many text-books on the eye, which do not aim to be devoted exclusively to eye surgery. The work, externally, is of good size, but this is found to be due to large print, and large pictures, many of which are entirely unnecessary, rather than to an abundance of valuable subject-matter. Surely no one capable of doing eye surgery need be shown, by means of a full-page photograph, how to illuminate the eye-field with a hand lens, nor need he be shown how to apply ointment to the conjunctival cul-de-sac. What's the need of showing an eye surgeon how to apply lid retractors, giving two full pages to illustrate this simple procedure? Even in the text a large amount of the subject-matter is devoted to the unnecessary description of commonplace steps. To recapitulate, the beginner will not need this work, and the eye surgeon will likely have at his finger's

end all the details mentioned so laboriously, long before he is likely to want a book of this title. We consider the real worth of this book small, and have been disappointed in its perusal.

Ophthalmic Semiology and Diagnosis. By CHARLES H. BEARD, M. D. Illustrated. $4. (*Philadelphia: P. Blackiston's Son & Co., 1913.*)

This is one of the most unsatisfactory books which has come to our attention recently. We recognize the fact that it is one of a number, which is embraced in the so-called "International System of Ophthalmic Practice," but we think that fact should not permit the desultory putting together of matter, as found in this volume. The author writes on subjects at his own whim, and lets others alone, of equal, or more importance. He does not limit himself either to the external diseases of the eye, or those visible with the ophthalmoscope, but has fragments, large and small, dealing with both; and then, too, most important omissions. There is a considerable amount of good matter on the retina, and its diseases, and so far as it goes the rest of the book is also good, but is not satisfactory in its present manner of presentation. Probably if the author had had his field more clearly defined for him he would have produced a work worth while, but in its present arrangement this book has but a limited sphere of usefulness.

Diseases and Injuries of the Eye. By WILLIAM GEORGE SYM, M. D., Edinburgh. Illustrated. $2.50. (*New York: The Macmillan Company, 1913.*)

This is a very satisfactory small work on the eye, and unlike a large number of others, is not an abbreviated edition of some of the larger text-books, but is distinctly the author's own work, and in it, at times, he expresses his own opinion, sometimes at variance with the accepted one, in rather a positive tone. Not that the author aims to be argumentative, but he is simply positive in his own opinion. This is just as well for the student, who is thereby receiving almost personal instruction from a well-informed teacher. The author skilfully introduces the required amount of pathology and bacteriology along with his subject-matter. As a text-book to round out the ordinary daily work of the student in the eye clinic this book will be found to be helpful and valuable, even though the said student may have to refer to some larger work for more thorough study of some of the rarer conditions met with there. As an exposition of clinical ophthalmology as viewed by a Scottish writer this work will afford additional interest to American readers. It is an excellent little work, well printed, well arranged, well illustrated, and its system of therapeutics is definite, safe and conservative, and may be safely followed.

The Difficulties and Emergencies of Obstetric Practice. By COMYNS BERKELEY, M. D., and VICTOR BONNEY, M. D. Illustrated. $7.50. (*Philadelphia: P. Blakiston's Son & Co., 1913.*)

This book differs from the usual text-book on obstetrics in that the authors have purposely omitted the physiology and management of normal pregnancy, labor and the puerperium, and confine their attention to the various abnormalities met with in the practice of obstetrics.

This book contains many excellent practical points for the student and practitioner, and more attention is given to the unusual disorders met with in obstetric practice than is possible in the usual text-book on obstetrics.

This book, however, is to be regarded rather as a practical guide, than a scientific work. Very scant reference is made to the literature, and there are no descriptions of the pathological and autopsy findings associated with abnormal conditions. Nor do the authors consider at any length the various unsolved problems met with in obstetrics.

The author's views on the toxæmias of pregnancy do not conform with the more modern teachings and they apparently regard all cases of eclampsia as being of nephritic origin.

Considerable space is devoted to the descriptions of the various obstetrical operations which are very good. As in most English works on obstetrics, the application of forceps to the sides of the pelvis, rather than to the sides of the child's head, is advocated.

The book is profusely illustrated with excellent original drawings.

Text-Book of Midwifery. By R. H. JOHNSTONE, M. D., etc. Illustrated. $3.50. (*New York: The Macmillan Company, 1913.*)

In this small hand-book the author has covered the subject of practical obstetrics in a thorough but concise manner, and the book ought to prove of value to the student of obstetrics as well as to the practitioner.

The arrangement of the subject-matter does not differ radically from that of the usual text-book on obstetrics, the author taking up in order the anatomy of the pelvis and female genitalia, conditions met with in normal pregnancy, labor and the puerperium, and then considering the various pathological conditions met with during the same periods. Lastly, there is a section devoted to the various obstetrical operations.

The chapters on the implantation and early development of the ovum, with the formation of the placenta, are from the student's standpoint particularly good, and the author presents this difficult subject in a short but comprehensive manner. The chapters on the mechanism of labor, and the management of normal labor are excellent, no details being omitted.

The author's description of the various obstetrical operations are rather brief and the indications for the various operations are not discussed as extensively as might seem wise. In common with most English authors, the writer, in his description of the various forceps operations, advocates the "pelvic" application of the forceps, instead of the method usually taught in American schools, namely, the application of the forceps blades to the sides of the child's head.

The illustrations in the book have been largely drawn from other text-books on obstetrics, due credit for which has been given to the various authors from whose works they are taken.

Text-Book of General Pathology. Edited by M. S. PEMBREY and J. RITCHIE. $5. (*New York: Longmans, Green & Co., 1913.*)

In this text-book, edited by Pembrey and Ritchie, an effort has been made to present general pathology from a physiological or functional standpoint. This effort is indicative of the recent trend of thought; the authors, however, among whom are many of the most prominent British pathologists and physiologists, must suffer the disadvantage of doing something novel and unaccustomed. The great difficulty is to preserve unity and proportion in such a vast subject.

In the preface the object of the work is stated, and it is added that, where the combined efforts of pathology and physiology have been unproductive, conventional lines are followed. As a consequence, the book is divided rather sharply into two parts, the one in the accustomed manner, the other showing the results of modern laboratory methods. The conventional chapters are gathered toward the beginning, the others at the end. In the first category the writers have done their work adequately. Inflammation is considered in a very full and clear manner, and the nervous system has a long chapter by Dr. Mott.

In the latter half of the book the material is more characteristic. Much data of an experimental nature bearing upon normal and abnormal body processes is included, and fruitless anatomical observations are avoided. The subjects are arranged in an unusual manner, the anatomical order being again ignored, and

functional entities grouped together. The chapter on respiration is especially pleasing and satisfactory, and may well serve as a model. Those upon degenerations, temperature, hepatic disease, carbohydrate metabolism, and gout, contain stores of useful and suggestive information for the student, presented fully in a clear and good style.

On the other hand, a few chapters, as those concerning digestion and circulation, fall below the general standard, while the kidney is much slighted. A little tendency is observed here and there to state opinions in such a way that they may possibly be mistaken for accepted facts.

Throughout this book a working knowledge by the reader of chemistry, physiology, and laboratory procedure is assumed. In this and in its general aim it is to be commended as a step in the proper direction.

A Clinical Manual of Mental Diseases. By FRANCIS X. DERCUM, M. D., PH. D. $3. (*Philadelphia and London: W. B. Saunders Company, 1913.*)

This book is based upon the annual course of lectures delivered by the author at the Jefferson Medical College. The classification adopted is exceedingly cumbersome, and unfortunately leads to a great deal of very unnecessary recapitulation.

The symptomotology of the various clinical entities is faithfully described, but it is all presented in such a formal way, without any case histories, and with practically no attention paid to more recent teachings in psychiatry that it is exceedingly unsatisfying. Particularly is this the case when one comes across such statements as: "Manic-depressive insanity is probably due to a toxin, the recoveries from the individual attacks suggest the formation of an antitoxin."

Then again it is rather surprising in this age to find hysteria considered in a chapter where mental diseases related to somatic affections are discussed.

In considering the eye-signs of general paralysis it is stated that in addition to the light reflex being lost that the reaction of accommodation is sooner or later involved, and then not content with this it is further emphasized that "the more advanced the case the more likely is there to be loss of accommodation, and in almost all cases the loss is present in both eyes simultaneously."

To allow him to make such statements the author's experience must surely be unique.

There are so many questionable statements made throughout the book that one could not conscientiously recommend it as a safe guide either for the physician or student.

Clinical Pathology. By P. N. PANTON, M. A., M. B. 446 pages. $4. (*Philadelphia: P. Blakiston Son & Co., 1913.*)

The author's attempt to produce a book intermediate in size between the larger and smaller works on "Clinical Pathology," which would meet the demands of the student and practitioner, has been unsuccessful, and for obvious reasons. Medical literature of the day has no legitimate place for this type of compend which sacrifices scientific accuracy and scope of statement to the ambition of including within one volume the subjects of blood-bacteriology, puncture fluids, urine, the alimentary system, the eye, skin, respiratory tract and histology. Of necessity, brevity of statement and the lack of detailed discussion, combined with the absence of any references to the literature, tend to foster the all too prevalent habit of drawing sweeping conclusions from insufficient data and for this reason especially the book is unsuited to the student. For the practitioner there exists a vast amount of indefinite disjointed statements, tests with scanty interpretations and a general arrangement of subject-matter calculated to discourage further reference to the book. Errors of omission are not uncommon—such as the absence of the polariscopic determination of sugar, newer methods of blood counting, or the estimation of the degree of pleocytosis in the cerebrospinal fluid. One and a half pages suffice to describe all forms of malaria. Such statements as are made with respect to the differentiation of amœbæ, the constancy of the amount of complement in guinea pig's serum, and the taking of 10 cc. of spinal fluid with impunity are a few of many questionable statements; while the six lines devoted to the Calmette reaction leave one with the feeling that the author is not aware of the real truth of the matter.

Illustrations, though few in number, are, for the most part good, and the text is quite free from typographical errors.

The Elements of Bacteriological Technique. By J. W. H. EYRE, M. D., etc. $3. (*Philadelphia and London: W. B. Saunders Company, 1913.*)

The second edition of Eyre's Bacteriological Technique rewritten and enlarged has just been published by Saunders. It consists of over five hundred pages, devoted entirely to the technique of bacteriology, divided into twenty-one sections.

These sections deal with such subjects as: Common glass apparatus, methods of sterilization, the microscope, staining methods, methods of identification and study, experimental animal inoculations and bacteriological analyses.

The material is presented in logical sequence, each subject being well described, and special attention being paid to all essential details. The illustrations are numerous and of considerable merit, each one having its own intrinsic value in being accurate and suggestive.

Several chapters deserve special note, as for instance, the opening chapter which gives a complete list of the glass apparatus commonly used in bacteriological work, and is followed by a useful consideration of the various methods of sterilization. The section entitled "The Microscope" affords a brief but comprehensive description of this instrument, and includes a discussion of the various accessories necessary for microscopical work. The section on "staining methods" is especially useful in giving a detailed description of the composition of the various dyes and all the latest methods of differential staining. A brief description with the classification of fungi preceding a short disussion on the life cycle of bacteria affords a splendid comparison between the two classes of microscopic life. Thus the relationship from the evolutionary standpoint is made clear. The chapter on "Methods of Identification and Study" is especially worthy of note. By a detailed study of the macroscopical, microscopical, biochemical and physical properties of various organisms a thorough and complete method for identifying them is given. The discussion on technique in relation to experimental animal work in bacteriology, though somewhat detailed, is worthy of considerable attention.

The treatise is concluded by a consideration of the technique of both quantitative and qualitative bacteriological analyses of water, milk, sewage and foodstuffs, which are highly important from the standpoint of practical or applied bacteriology. The methods outlined are the ordinary methods universally employed without any additional new ones.

This text-book is primarily intended as a laboratory guide for beginners. It may be highly recommended for the purpose for which it was primarily intended, as it is exceedingly thorough and gives all of our important modern methods.

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